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**A Randomized, Double-Blind, Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Illness**

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## 1.0 List of Abbreviations

AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
BDI-II	Beck Depression Inventory II
BPI-S	Brief Pain Inventory—Short Form
C	Celsius
CI	Clinical Investigator(s) (e.g. therapists, co-investigators)
CPK	Creatine phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DAP	Death Attitudes Profile
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
ECG	Electrocardiogram
ED	Emergency Department
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
F	Fahrenheit
FACIT	Functional Assessment of Chronic Illness Therapy Scale
FDA	Food and Drug Administration
FFMQ	Five-Facet Mindfulness Questionnaire
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IR	IR
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intra-venous
LSD	d-Lysergic acid diethylamide
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine oxidase Inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin

MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-Methylenedioxymethamphetamine
MP-1	MAPS' first clinical trial of MDMA-assisted psychotherapy for PTSD
OASIS	Overall Anxiety Severity and Impairment Scale
ORF	Observer Rating Form
PRN	As Needed
PSQI	Pittsburgh Sleep Quality Index
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTGI	Posttraumatic Growth Inventory
PTGI-C	Posttraumatic Growth Inventory—Caregiver Form
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SCID-RV	Structured Clinical Interview for DSM-IV Research Version
SCS	Self-Compassion Scale
SERT	Serotonin Transporter
SL	Sublingual
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SOCQ	States of Consciousness Questionnaire
PPQ	Psychological Process Questionnaire
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State-Trait Anxiety Inventory
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

## **2.0 Introduction, Background, and Rationale**

### **2.1 Introduction**

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval as a clinical trial sponsor for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) to assist psychotherapy. Currently MAPS is conducting a global series of Phase 2 clinical trials designed to evaluate the safety and efficacy of MDMA-assisted psychotherapy in treating Posttraumatic Stress Disorder (PTSD). This study will explore the use of MDMA in an additional indication for anxiety and stress disorders, related to end of life. This study is a randomized, double-blind, placebo-controlled exploratory pilot study of MDMA-assisted psychotherapy for anxiety in people with a life-threatening illness that is ongoing or with the possibility of recurrence.

The ongoing studies using MDMA-assisted psychotherapy in the treatment of PTSD will be used to inform the safety and dosing aspects of this new investigation of a potential therapy that could benefit the quality of life of adults with end-of-life anxiety. MAPS has published results showing clinically and statistically significant improvements in PTSD severity from twenty subjects treated in their first pilot study (MP-1) in the United States (U.S.) [1]. Findings from the long-term follow-up of MP-1 subjects suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [2]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) in twelve subjects suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance [3]. Long-term follow-up data, twelve months later, suggest that therapeutic benefits continued to increase in this subject population.

This exploratory placebo-controlled study is designed to investigate the safety and feasibility of MDMA-assisted therapy in 18 adults who have a prognosis for at least nine months life expectancy and currently have anxiety related to a life-threatening illness that is ongoing or is in remission with the possibility of recurrence. This partial cross over study will assess safety and obtain estimates of effect size in response to two experimental sessions of MDMA-assisted therapy in comparison to an inactive placebo control. Outcomes will include treatment-related changes in anxiety, depression, sleep quality, quality of life, self-reported and observer-reported changes in attitudes, attitudes toward death and the prospect of death, and changes in self-compassion and self-reported mindfulness. Results from this study, if promising, will inform the dose, end points and treatment regimen for subsequent studies. This study is also intended to develop a manualized psychotherapeutic approach to this potential treatment.

### **2.2 Background**

#### **2.2.1 Anxiety Related to Life-Threatening Illness**

Individuals facing, or who have faced, a life-threatening illness contend with more than just the physical symptoms of their condition. Anxiety, depression, anger, and despair often exacerbate the distress already caused by the illness itself, and can significantly

increase caregiver distress as well [4]. End-of-life problems, including pain management, are increasingly recognized by caregivers and the public as significant public health concerns [5-7]. Research suggests that diagnosis of, and living with a life-threatening illness can result in symptoms similar to those seen in Posttraumatic Stress Disorder (PTSD), and that these symptoms may persist even if the individual recovers, or their illness goes into remission [8, 9]. These symptoms may include emotional avoidance and numbing, difficulty relating to or connecting with friends or loved ones, difficulty sleeping, a sense of foreshortened future, and intrusive thoughts or memories related to the illness.

While efforts to enhance palliative care for the terminally ill have improved greatly over the last several decades, and significant strides have been made in reducing individuals' physical pain and discomfort, less progress has been made in helping individuals reduce or come to terms with the psychological and existential issues raised by their condition. Fears of loss of autonomy, helplessness, and death itself are also often accompanied by challenging internal family dynamics that surface around the end of life. In a 2003 report, McClain et al. [10] support developing additional palliative care interventions to improve the well-being of people with terminal illness by "...keeping the psychological distress of patients who are facing death to a minimum. What is less clear, however, is whether interventions exist that can help raise a terminally ill individual's sense of spiritual well-being."

Given that in this situation, spiritual, familial, psychological, and existential concerns all take a position of primary and imminent importance for many people, the development of new treatment modalities to meet these needs is a clear imperative. Enabling individuals to face life-threatening illness and all of its concomitant difficulties with dignity, creativity, love, support, and kindness is the primary impetus for this research study.

### **2.2.2 MDMA**

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 [11, 12]. MDMA is a monoamine releaser that has its greatest effects on serotonin, followed by norepinephrine and dopamine [13-18]. MDMA is capable of inducing unique psychopharmacological effects, including:

- Decreased feelings of fear
- Increased feelings of wellbeing
- Increased sociability and extroversion
- Increased interpersonal trust
- Alert state of consciousness

Early observers noted increased acceptance of self and others, increased tolerance of emotionally upsetting materials, and the ability to address these issues without extreme disorientation or ego loss [19-22]. In the U.S., MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists, including this study's Principal Investigator (PI) and other therapists in the treatment of neuroses, relationship problems,

and PTSD [19, 20, 23, 24] before it was placed in Schedule 1 in 1985, as a result of the DEA's concern for extensive non-medical use [22, 25, 26]. Placement in Schedule 1 prohibited it for use, except in a federally-approved research setting.

In contrast to daily administrations of SSRIs, MDMA-assisted psychotherapy consists of several drug-assisted sessions interspersed with a moderate course of non-drug psychotherapy. Thus the effects of MDMA are distinct from and go well beyond those of anti-anxiety drugs such as benzodiazepines. Furthermore, there is no evidence that MDMA creates a physical dependency, as benzodiazepines do. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of ecstasy (material represented as containing MDMA) [27, 28]. Studies of regular or problematic ecstasy users indicate that on average, regular use occurs no more often than once a week [29]. Hence, MDMA may have moderate abuse potential. See the Investigator's Brochure (IB) for a more detailed explanation.

### **2.2.3 Previous Clinical Experience with MDMA**

Classification as a Schedule 1 drug hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and effectiveness of MDMA-assisted psychotherapy has become more feasible due to an open IND with the FDA [30-32]. The first double-blind, placebo-controlled U.S. Phase 1 study sanctioned by the FDA was conducted in 1994, with findings that suggested MDMA caused a significant increase in body temperature and heart rate in some healthy volunteers [33]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting [33]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [33-39]. The elevation in body temperature noted in healthy volunteers was not clinically significant in the sponsor's proof-of-principle MP-1 study comparing MDMA to placebo in subjects with PTSD [1].

The potentially therapeutic effects of MDMA were initially investigated starting in 2000, in a MAPS-sponsored dose response pilot study in Spain, in women survivors of sexual assault with treatment-resistant PTSD [40, 41]. Unfortunately, the study in Spain was halted in 2002 due to political pressure from the Madrid Anti-Drug Authority. Prior to its suspension, six women who were enrolled and treated in this study with single doses ranging from 50 mg to 75 mg demonstrated mild signs of improvement without any adverse events (AEs) or signs of deteriorating mental health [41].

MAPS went on to sponsor the first randomized, placebo-controlled Phase 2 pilot study of MDMA-assisted psychotherapy for the treatment of chronic, treatment resistant PTSD, which demonstrated promising results in a sample of 20 subjects [1]. Findings from the long-term follow-up of this study indicate that the therapeutic benefits have been sustained over time on average, although two subjects experienced a relapse in PTSD symptoms [2]. The sponsor also supported a randomized, double-blind pilot study in 12 subjects with chronic, treatment-resistant PTSD in Switzerland, which found a trend toward significant improvement in subjects receiving 125 mg MDMA at two-month

follow-up, when compared to a 25 mg active placebo MDMA. The improvement continued to increase during the twelve-month follow-up [3]. These studies have shown promise for MDMA-assisted psychotherapy to help people overcome PTSD, an anxiety-related disorder, that suggest this treatment could also be useful in treating anxiety associated with end-of-life issues.

As of July 2014, MDMA has been administered to more than 1080 research subjects, in both Phase 1 and Phase 2 studies, with only a single occurrence of a drug-related SAE, and no unexpected related SAEs [1, 3, 13, 16, 25, 33, 34, 36, 37, 39, 40, 42-85].

#### **2.2.4 MDMA-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Illness**

A small body of research, mainly conducted in the 1950s and 1960s prior to the placement of most psychedelic drugs into Schedule 1, suggests that therapeutic interventions involving psychedelics such as LSD, psilocybin, and MDMA may help to address the personal, interpersonal, and existential issues that present during the course of a life-threatening illness [86-91]. MDMA shares with the ‘classical’ psychedelics LSD and psilocybin the ability to produce perceptions of new meanings for thoughts and objects [92], and increases tolerance for confronting negative memories [93]. Narrative reports support its use as a psychotherapeutic adjunct [94-97].

Prior to placement into Schedule I, MDMA was used in combination with psychotherapy in the treatment of neuroses, relationship problems, and PTSD [20, 22, 24]. It was also used in the treatment of some individuals with chronic pain [19, 98], and in individuals with advanced cancer [19, 94-96, 98]. Case reports and narrative accounts of MDMA-assisted therapy indicate that the treatment was often successful [19, 20, 22, 23, 99, 100]. A discussion of MDMA-assisted psychotherapy and a discussion of several case studies appeared in a peer-reviewed journal [19].

MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA as a pharmacological adjunct that may enhance or amplify certain aspects of psychotherapy. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD and anxiety patients [37, 63, 66, 67, 85, 93, 101-103].

In a psychotherapeutic context, MDMA was reported to produce a lowering of defenses and greater ability to think about and reflect on distressing thoughts and feelings [19, 21, 22, 76]. When spending time with loved ones, individuals who took MDMA in therapeutic contexts often spent time discussing painful or emotionally sensitive topics, such as the impending death of a loved one in the advanced stages of cancer [94-97]. Reduction in pain was often reported [19, 94-97, 104].

Treatment goals of MDMA-assisted psychotherapy for anxiety associated with life-threatening illness include alleviating symptoms, as well as helping individuals find a perspective and orientation toward death and remaining life that supports well-being,

creativity, love, compassion, and dignity. The biologic and psychotherapeutic approaches are intended to overlap and reinforce each other. Knowledge about the connections between the neurobiological and therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala [101] and attenuates amygdalar response to angry faces [67]. This action is compatible with its reported reduction in fear or defensiveness and is in contrast to the stimulation of the amygdala which is observed in animal models of conditioned fear, a state similar to PTSD [105-107]. The reduction in stress-induced activation of the amygdala may be supported and enhanced by interacting with the therapists during and after the MDMA experience.

Oxytocin is a neurohormone associated with pair bonding and social affiliation in mammals [108]. Oxytocin administration is associated with increased interpersonal trust and attenuated reactivity to threatening faces [108-110]. Some researchers have suggested a role for oxytocin in treating PTSD [111]. MDMA has been shown to elevate serum oxytocin in humans [37, 112]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [67]. The effects of MDMA on oxytocin may influence empathy or compassion for self and others, decrease defensiveness, and strengthen therapeutic alliance. These factors taken together can provide the opportunity for a corrective emotional experience [19].

A combined treatment of MDMA and psychotherapy may be especially useful for treating anxiety disorders because MDMA can attenuate the fear response of a perceived threat to one's emotional integrity and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion [1, 20, 22, 41]. This reduction in defensiveness may permit a deeper engagement with material that would otherwise be too distressing to face. Subjects are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. MDMA seems to engender internal awareness that even painful feelings that arise are an important part of the therapeutic process. In addition, feelings of empathy, love, and deep appreciation often emerge, along with a clearer perspective of present difficulties, a more accurate perspective about their significance, and a heightened awareness of the support and safety that exists in the present. As a result, MDMA-assisted psychotherapy may enable the subjects to restructure their intra-psychic realities and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

A comprehensive review of MDMA research is included in the IB supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

### **2.3 Protocol Purpose**

This Phase 2 pilot study is a randomized, double-blind placebo-controlled study in 18 subjects comparing the effects of placebo and active dose MDMA as an adjunct to psychotherapy. Thirteen subjects will be randomized to the active dose condition of 125 mg of MDMA and five subjects will be randomized to the placebo condition. The study will consist of two blinded experimental sessions of MDMA-assisted psychotherapy or

placebo, each lasting six to eight hours and scheduled two to four weeks apart, within a moderate course of non-drug psychotherapy. Each study subject will be unblinded one month after their second experimental session in Stage 1 after completion of outcome measures, which constitutes the Primary Endpoint assessment for that subject.

After unblinding, subjects receiving placebo will have the opportunity to cross over to open-label Stage 2 and only subjects receiving active dose MDMA will complete the third open-label experimental session. The primary outcome measure will be completed via subject self-report at Baseline, at the Primary Endpoint one month after the second experimental session, and at the End of Stage 1 visit, one month after the third open-label experimental session, and at equivalent points in Stage 2. Some secondary outcome measures will be administered by a blinded Independent Rater, while others will be completed by subjects' self-report. This study will provide an estimate of effect size based on response of anxiety symptoms to MDMA-assisted psychotherapy.

The PI and a co-therapist, along with supervised intern therapists will conduct psychotherapy visits in male/female therapy teams.

## 2.4 Rationale of Dose Selection

This study will compare the effects of psychotherapy sessions assisted by placebo or active dose MDMA. Placebo will consist of lactose. The active dose will be 125 mg MDMA, followed one and half to two and a half hours later by an optional supplemental dose of 62.5 mg.

**Table 1. MDMA Dose Regimen**

	<b>Initial Dose</b>	<b>Optional Supplemental Dose</b>	<b>Cumulative Dose (Initial + Supplement) per Session</b>
<b>Placebo</b>	0 mg	0 mg	0 mg
<b>Active Dose</b>	125 mg	62.5 mg	187.5 mg

The active dose of MDMA to be used in this study is identical to those used in previous studies in the U.S., Switzerland, and Israel [1]. Previous researchers have also used doses within this range [33, 34, 36, 38, 54, 113-117]. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy [20, 22, 25]. The initial active dose is expected to produce all the commonly reported effects of MDMA. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose.

## 3.0 Protocol Objectives

The overall objective of this study is to examine whether an active dose of MDMA versus a placebo used in conjunction with psychotherapy will reduce or attenuate anxiety

and depression symptoms, and improve quality of life as evaluated by standard clinical measures and to collect safety data.

### **3.1 Primary Objective**

The primary objective of the study is to assess changes in trait anxiety in subjects receiving active dose MDMA compared to those receiving placebo as measured by STAI-Trait scores at Baseline and the Primary Endpoint, one month after the second experimental session.

### **3.2 Secondary Objectives**

The additional objectives of the study involve comparing subjects receiving active dose MDMA to those receiving placebo for the following exploratory objectives:

- Assess changes in self-reported State Anxiety symptoms as measured with the State-Trait Anxiety Inventory—State subscale (STAI-State) from Baseline to the Primary Endpoint.
- Assess changes in self-reported depression symptoms with the Beck Depression Inventory- II (BDI-II) from Baseline to the Primary Endpoint.
- Assess changes in clinician ratings of depression symptoms with the Montgomery-Asberg Depression Rating Scale (MADRS) from Baseline to the Primary Endpoint.
- Assess changes in quality of life with Functional Assessment of Chronic Illness Therapy Scale (FACIT-Sp) from Baseline to the Primary Endpoint.
- Assess changes in global functioning with the Global Assessment of Functionality (GAF) from Baseline and the Primary Endpoint.
- Assess changes in self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) from Baseline to the Primary Endpoint.
- Assess changes in subjects' attitudes toward death with the Death Attitudes Profile (DAP) from Baseline to the Primary Endpoint.
- Assess personal growth with the Post-Traumatic Growth Inventory (PTGI) from Baseline to the Primary Endpoint.
- Assess caregiver perceptions of subjects' personal growth with the Post-Traumatic Growth Inventory—Caregiver Form (PTGI-C) from Baseline to the Primary Endpoint.
- Assess changes in self-oriented compassion with the Self-Compassion Scale (SCS) from Baseline to the Primary Endpoint.
- Assess changes in self-reported mindfulness with the Five-Facet Mindfulness Questionnaire (FFMQ) from Baseline to the Primary Endpoint.

The following objectives will include exploratory analyses intended to inform protocol design:

- Explore the effects of each experimental session with active dose MDMA or placebo upon self-reported changes in consciousness, as those associated with a

transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).

- Explore the effects of each experimental session upon self-reported cognitive and emotional processing via the Psychological Process Questionnaire (PPQ).
- Assess the effect of the third experimental session using a within-subject comparison of the Primary/Secondary Endpoint to 1-month follow-up assessment in active dose subjects using STAI-Trait, STAI-State, MADRS, BDI-II, DAP, GAF, FFMQ, PTGI, PSQI, PTGI-C, SCS, and FACIT.
- Conduct a within-subject analysis comparing Stage 1 and Stage 2 in placebo subjects using STAI-Trait, STAI-State, MADRS, BDI-II, DAP, GAF, FFMQ, PTGI, PTGI-C, PSQI, SCS, and FACIT at the Primary and Secondary Endpoints.
- Assess durability of changes in outcome measures using STAI-Trait, STAI-State, MADRS, BDI-II, DAP, GAF, FFMQ, PTGI, PTGI-C, PSQI, SCS, and FACIT at the 6-month and 12-month follow-up visits.
- Assess qualitative reports of subjects' experiences in the study via a semi-structured interview at the 1-month follow-up assessment.
- Assess observations of the subject's overall state of being from up to three observers using the Observer Rating Form (ORF) at Baseline, the Primary Endpoint, and the 6- and 12-month follow-up visits.
- Assess the ability of the Clinical Investigator(s) (CI) and subjects to accurately guess condition assignment in Stage 1.

### 3.3 Safety Objectives

The safety objectives of the study are to monitor and assure safety of subjects during and after the experimental sessions by assessing physiological effects, psychological distress, adverse events, spontaneously reported reactions, and suicidality.

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during visits prior to experimental sessions, twice during experimental sessions, and several times after each experimental session, with comparisons made between subjects in each condition.
- Subjective Units of Distress (SUD) and vital signs including blood pressure, heart rate, and temperature will be measured during each experimental session. Vital signs will be compared between subjects in each condition.
- Changes to pre-existing chronic pain symptoms, when applicable, will be collected using the Brief Pain Inventory—Short Form (BPI-S) at Baseline and throughout the study, with comparisons made for Primary Endpoint, end of Stage 1 or Stage 2 and 6- and 12-month follow up.
- Serious adverse events (SAEs), adverse events, and spontaneously reported reactions will be collected during the study according to Section 8.5.

### 4.0 Protocol Design

This is a randomized, double-blind, placebo-controlled pilot study that will examine the safety and efficacy of MDMA-assisted psychotherapy in subjects diagnosed with anxiety

associated with a life-threatening cancer or non-dementing neurological illness, which may be ongoing or in remission but with the possibility of recurrence. Stage 1 will include two blinded and one open-label MDMA-assisted psychotherapy sessions scheduled two to four weeks apart with a male/female co-therapist team. Therapy teams will consist of varying combinations of the Principal Investigator, experienced co-therapists, and intern co-therapists. Subjects will be treated by the same therapy team throughout their participation in the study. There will also be a moderate course of preparatory sessions and integrative sessions, as described in the Time and Events Table.

Upon enrollment, subjects will be randomly assigned to receive either placebo (five subjects) or active dose (thirteen subjects) MDMA. In Stage 1, subjects will meet with their therapist team for three preparatory sessions and two blinded experimental sessions of MDMA-assisted psychotherapy. After each experimental session, subjects will stay overnight at the site and complete an integrative session the next day, followed by daily telephone calls for the next seven days and two additional integrative sessions. One month after the second experimental session, the Primary Endpoint assessment will take place, after which the blind will be broken. All subjects who received the active dose will then receive a third open-label experimental session with active dose MDMA. Subjects who receive the placebo will be offered the option to continue to the open-label Stage 2, unless they meet any exclusion criteria for study participation. In Stage 2, subjects will receive active dose MDMA in three experimental sessions that will otherwise follow the same sequence of events after a single preparatory session. (See Time and Events Table).

A blinded Independent Rater will administer the MADRS and the GAF; all other outcome measures will be collected via subjects' self-report or via report provided by a caregiver or observer.

Anxiety symptoms will be assessed in all subjects throughout Stage 1, and anxiety symptoms will be assessed throughout Stage 2 for subjects continuing on to Stage 2. All subjects will complete a follow-up occurring one month after their third experimental session in Stage 1 for active dose subjects, and one month after their third experimental session in Stage 2 for subjects who received placebo in Stage 1. In addition all subjects will complete visits six months and then 12 months after their final experimental session where outcome measures and a questionnaire on any lasting benefits or harms of the treatment will be administered. (See Time and Events Table)

The sponsor will conduct an ongoing review of video data of psychotherapy sessions, entry criteria, vital signs, and reaction data for completed sessions and any AEs. The sponsor will provide ongoing feedback to the co-therapist teams to ensure proper therapist training, subject safety, and to support the sponsor's effort to manualize MDMA-assisted psychotherapy for this indication.

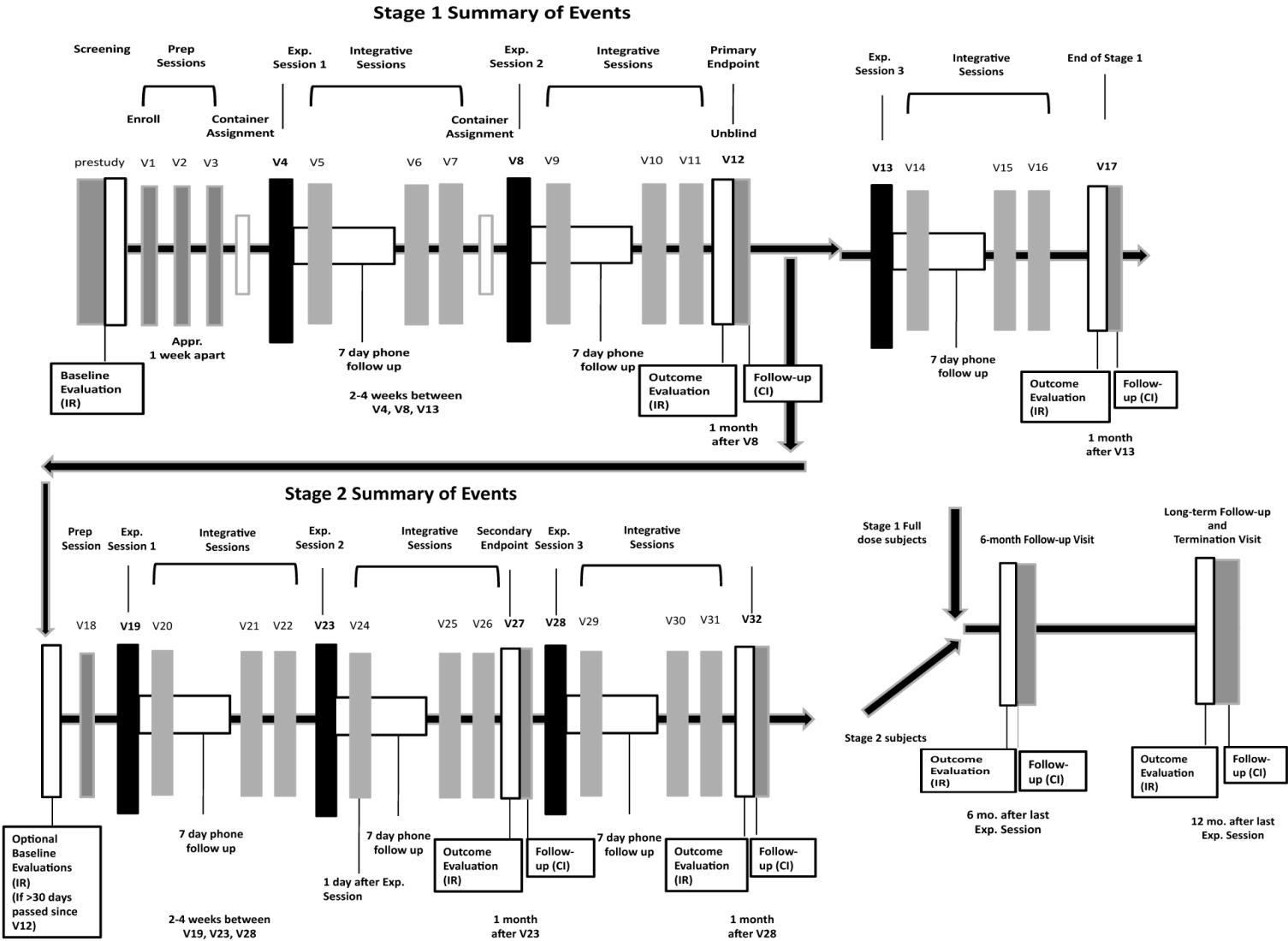


Table 2.Stage 1 Time&Events	Preparatory		Experimental Session 1	Experimental Session 2			Experimental Session 3	Follow-Up		
Visit #	Pre-Study	V 1,2,3	V4	V 5,6,7	V8	V 9,10,11	V12	V13	V 14,15,16	V17
Type of Visit	Screening may take place over more than one day	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Primary Endpoint	Experimental Session 3	Integrative Sessions	End of Stage 1 & Outcome
Visit Timing or Study day or Window	Up to 2 months prior to Visit 1	Prior to V4	Up to 5 weeks post V1	Before V8 <sup>A</sup>	2-4 weeks post V4	Before V12 <sup>A</sup>	1 month +/- 1 week post V8	3-4 weeks post V8 <sup>N</sup>	Before V17 <sup>A, N</sup>	May happen over > 1 day. 1 mo. +/- 1 week post V13 <sup>N</sup>
Initial Phone Screen	✓									
Informed Consent	✓									
Medical/Psychiatric History	✓									
General Phys. Exam (BP, Pulse, Temp)	✓									
Brief Neurological Exam	✓									
ECG	✓									
SCID-RV	✓									
Clinical Lab Tests, w/ HIV, HCV test	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medication Taper (if applicable)	✓									
Study Enrollment after meeting I/E		✓ <sup>G</sup>								
Record to Audio/Video		✓	✓	✓	✓	✓	✓	✓	✓	✓
General Well-Being		✓	✓	✓	✓	✓		✓	✓	
Drug Screen	✓		✓		✓			✓		
Pregnancy Screen (if applicable)	✓		✓		✓			✓		
Complete Randomization Procedure			✓ <sup>B</sup>							
STAI-Trait	✓						✓			✓
STAI-State	✓	✓ <sup>I</sup>					✓			✓
BDI-II	✓			✓ <sup>L</sup>			✓			✓
BPI-Short		✓ <sup>I</sup>		✓ <sup>K</sup>		✓ <sup>K</sup>	✓		✓ <sup>K</sup>	✓
GAF, MADRS		✓					✓			✓
DAP, PTGI, PTGI-C PSQI		✓ <sup>G</sup>					✓			✓
FFMQ, SCS		✓ <sup>H</sup>					✓			✓
FACIT		✓ <sup>I</sup>					✓			✓
ORF	✓						✓			
C-SSRS	✓	✓	✓ <sup>C, D, E</sup>	✓ <sup>J, M</sup>	✓ <sup>C, D, E</sup>	✓ <sup>J, M</sup>	✓	✓ <sup>C, D, E</sup>	✓ <sup>J, M</sup>	✓
Administer IP Drug + Therapy, SOCQ, PPQ			✓		✓			✓		
Monitoring of BP, Pulse and Temp.			✓		✓			✓		
SUD			✓ <sup>F, E</sup>		✓ <sup>F, E</sup>			✓ <sup>F, E</sup>		
Beliefs of Condition Assignment				✓ <sup>K</sup>		✓ <sup>K</sup>			✓ <sup>K</sup>	
Overnight Stay			✓		✓			✓		
Integrative Therapy Session				✓		✓			✓	
7 days Integrative Telephone Contact				✓ <sup>J</sup>		✓ <sup>J</sup>			✓ <sup>J</sup>	
AEs Requiring Medical Attention			✓	✓	✓	✓	✓	✓	✓	✓
Spont. Reported Reactions and all AEs			✓	✓	✓	✓		✓	✓	
AEs of psychiatric status or withdrawal		✓	✓	✓	✓	✓	✓	✓	✓	✓
Serious Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓
Issue Memory Aid Card										✓
Semi-Structured Interview										✓
Unblinding <sup>J</sup>							✓			

A =First Integrative session is 1 day after exp session B = At least 24 hrs prior to 1st exp. session C =Approximately 6 hours post MDMA D =At the beginning of the session E =As needed  
F=Approximately every 90 minutes G =Given on 1<sup>st</sup> preparatory session (V2) H= Given on 2<sup>nd</sup> preparatory session (V1) I= Given on 3<sup>rd</sup> preparatory session (V3) J =For 7 days post Exp. Session, C-SSRS D2 and D7 of calls only, General well being for all 7 days. K= On the day of the 1<sup>st</sup> integrative session following the Exp. Session L=On the third integrative session after the first experimental session only. M= Given at all three integrative sessions

Table 3. Time & Events Stage 2	Preparatory Session	Experimental Session 1		Experimental Session 2		Secondary Endpoint	Experimental Session 3		End of Stage 2		Long-term Follow-up
Visit #	V18*	V19	V20,21,22	V23	V24,25,26	V27	V28	V29, 30, 31	V32		LTFU
Type of Visit	Preparatory	Experimental	Integrative	Experimental	Integrative	Outcome	Experimental	Integrative	Outcome		Follow-up
Visit Timing	Within 1 month post V12*	1 week post V18	Between V19 and V23	2-4 weeks post V19	Between V23 and V27	1 month +/- 1 week post V23	3-4 weeks post V23	Between V28 and V32	1 month +/- 1 week post V28		6 months AND 1 year post V13 or V28
Confirm Informed Consent	✓										
Confirm Inclusion/Exclusion	✓										
Enrollment in Stage 2	✓										
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Record to Audio/Video	✓	✓	✓	✓	✓		✓	✓			
General Well-Being	✓	✓	✓	✓	✓	✓	✓	✓			
Drug Screen		✓		✓			✓				
Pregnancy Screen (if applicable)		✓		✓			✓				
STAI-Trait, MADRS	Use V12*					✓ <sup>H</sup>			✓		✓
STAI-State, GAF, DAP, PTGI, PTGI-C PSQI, FFMQ, SCS, FACIT	Use V12*					✓			✓		✓
BDI-II	Use V12*		✓ <sup>J</sup>			✓			✓		✓
BPI-Short	Use V12*		✓ <sup>I</sup>		✓ <sup>I</sup>	✓		✓ <sup>I</sup>	✓		
ORF						✓					✓
C-SSRS	✓	✓ <sup>B,C,D</sup>	✓ <sup>G,K</sup>	✓ <sup>B,C,D</sup>	✓ <sup>G,K</sup>	✓	✓ <sup>B,C,D</sup>	✓ <sup>G,K</sup>	✓		✓
Administer Drug + Therapy		✓		✓			✓				
Monitoring of BP, Pulse, and Temp.		✓		✓			✓				
SUD		✓ <sup>D,E</sup>		✓ <sup>D,E</sup>			✓ <sup>D,E</sup>				
Overnight Stay, SOCQ, PPQ		✓		✓			✓				
Integrative Therapy Session			✓ <sup>A</sup>		✓ <sup>A</sup>			✓ <sup>A</sup>			
Seven Days Telephone Contact			✓		✓			✓			
AEs Requiring Medical Attention	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Spont. Reported Reactions and all AEs		✓	✓ <sup>F</sup>	✓	✓ <sup>F</sup>		✓	✓ <sup>F</sup>			
AEs of psychiatric status or withdrawal	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Serious Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Complete Stage 2 go to follow-up									✓		
Issue Memory Aid Card									✓		
Semi-Structured Interview									✓		
Follow-up Questionnaire											✓ <sup>L</sup>
Termination Visit											✓ <sup>L</sup>

\* If Visit 18 is more than 30 days after Visit 12, then subjects will need to repeat measures prior to starting Stage 2.

A = First session is one day after experimental session; B = Approximately six hours post MDMA; C = At the beginning of the session; D = As needed; E = Approximately every 90 minutes; F = Reactions collected for seven days post experimental session; G = Day 2 and Day 7 phone calls only; H = 2 weeks after the second experimental session but before the third experimental session; I = On the day of the first integrative session following the Exp. Session; J=At the third integrative session following the first experimental session only; K=At all three integrative sessions; L=At the 12-month follow-up visit only.

#### **4.1 Planned Duration of Study**

Subjects enrolled in this study will fall into two categories that will determine the duration of the study.

1. Subjects receiving active dose MDMA completing Stage 1 only: 15 months or 18 visits, including active participation for 3.5 months plus long-term follow-up visits at six and 12 months after the last experimental session.
2. Subjects receiving placebo who continue and complete Stage 2: 18 months or 29 visits, including active participation for six months plus long-term follow-up visits at six and 12 months after the last experimental session.

Screening may take up to two months. The time period between the End of Stage 1 and the start of Stage 2 should be one month and is not to exceed five months for any subject. Any delay between visits would result in a corresponding extension of study duration.

#### **4.2 Recruitment and Subject Population**

Subjects may be men or women aged 18 or older with significant anxiety related to a diagnosis of a life-threatening illness. The illness can be current or have the possibility of recurring. Subjects should be diagnosed with cancer or a life-threatening, non-dementing neurological illness, and have a prognosis of at least nine months' life expectancy in order to enter the study. Subjects will be recruited through printed ads, internet ads, referrals from other psychiatrists, psychotherapists or physicians, and through word of mouth. Eighteen subjects who meet all inclusion criteria without meeting any exclusion criteria will be admitted to the study. Only IRB-approved recruitment materials and advertisements will be used for the study.

##### **4.2.1 Inclusion Criteria**

Individuals eligible to be enrolled into this protocol:

1. Have received a diagnosis of a life-threatening cancer or non-dementing neurological illness, which may be ongoing or in remission but with the possibility of recurrence;
2. Have a prognosis of at least nine months' life expectancy from the time of screening;
3. Have a score of 45 or higher on the STAI-Trait, indicating moderate to severe anxiety;
4. If the individual has a documented history of anxiety disorder, the patient and investigator are in agreement that the individual's present anxiety is primarily resultant from or exacerbated by their illness;
5. May have a concurrent affective disorder, excepting bipolar affective disorder 1;
6. Are at least 18 years old;

7. If in ongoing psychotherapy at the time of recruitment, are able to continue to see their outside therapist during the course of the study. Subjects must sign a release permitting the CI to communicate directly with their therapist;
8. If currently prescribed medications or medical interventions by a physician related to treatment of their illness, subjects must agree to permit the CI to communicate directly with their prescribing physician;
9. Are willing to refrain from changing therapists, increasing the frequency of therapy, or commencing any new type of therapy until after the evaluation session at the End of Stage 1 or 2, as applicable;
10. Are willing to refrain from taking any psychiatric medications during the study period (defined as the period commencing with enrollment in the study through the follow-up visit one month after the final experimental session), with the exception of gabapentin when prescribed for pain control. Individuals using opiates for pain management will be asked to decrease the dose or avoid taking their pain medication for 24 hours prior to experimental sessions if possible, as these medications may reduce the efficacy of MDMA. Subjects will be permitted to take their prescribed opiate medication during this period if necessitated by pain flare-ups. If the subject is on stimulants for ADHD at Baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives and one week for symptom stabilization before each experimental session and do not restart for ten days after each experimental session. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician;
11. Agree to refrain from taking, for one week preceding each experimental session:
  - a. Any herbal supplement (except with prior approval of the research team).
  - b. Any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen, unless with prior approval of the research team).
  - c. Any prescription medications (with the exception of birth control pills, thyroid hormones, or other medications approved by the research team);NOTE: Must have physician's approval  
Exceptions will be made for medications necessary for the ongoing treatment of life-threatening illnesses, as per the PI in consultation with treating physicians;
12. Agree to take nothing by mouth except alcohol-free liquids after midnight the evening before the experimental session;
13. Agree to refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within twenty-four hours of each experimental session;
14. Agree not to use caffeine or nicotine for two hours before and six hours after ingesting the drug or until the therapists deem it safe to do so;
15. Are willing to commit to medication dosing, experimental sessions, follow-up sessions, and to complete evaluation instruments;
16. Are willing to remain overnight at the study site after each experimental session until after the integrative session occurring the next morning;

17. Are willing to be driven home the morning after the experimental sessions, after the integrative session either by a driver arranged by the subject or by the site personnel or taxi;
18. Are willing to be contacted via telephone on a daily basis by one of the therapists for a week after each experimental session;
19. Are willing to provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by CI in the event of a subject becoming suicidal;
20. Are willing to select up to three observers who will complete observer measures of subject attitudes and behavior;
21. Agree to inform the CI within 48 hours of any planned medical interventions;
22. Are willing to refrain from participating in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period;
23. If female subjects of childbearing potential, must have negative pregnancy test results, be willing to have pregnancy tests, and must agree to use an effective form of birth control during the treatment period;
24. Are proficient in speaking and reading English;
25. Agree to have all psychotherapy sessions recorded to audio/video.

#### **4.2.2 Exclusion Criteria**

Individuals not eligible to be enrolled into this protocol are those who:

1. Are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control;
2. Have a history of, or current primary psychotic disorder or bipolar affective disorder type 1 or a personality disorder that, in the opinion of the investigator, would interfere with the patient's participation in the study;
3. Are diagnosed with dissociative identity disorder or an eating disorder with active purging;
4. Have evidence or history of significant (controlled or uncontrolled) cerebrovascular or cardiovascular disease, primary or metastatic tumors in the brain, renal disease, or any other medical disorder judged by the CI to significantly increase the risk of MDMA administration (Subjects with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded);
5. Are diagnosed with a dementing neurological illness;
6. Are experiencing cognitive and/or affective deficits as a result of chemotherapy that, in the opinion of the investigator, would interfere with the subject's ability to participate in the study;
7. Subjects who are receiving primary treatment for their illness such as initial chemotherapy or radiation, or who are recovering from surgery will be excluded. Subjects in ongoing maintenance treatment will be considered on a case by case basis and will be excluded if the CI, in consultation with the prescribing physician, judges that the maintenance drug is likely to lead to adverse drug interactions;

8. Have hypertension using the standard criteria of the American Heart Association (values of 140/90 or higher assessed on three separate occasions);
9. Have evidence or history of liver disease that would affect metabolism of MDMA;
10. Have diabetes type I or II;
11. Have history of hyponatremia or hyperthermia;
12. Weigh less than 48 kg;
13. Would present a serious suicide risk, as determined through psychiatric interview, responses to CSSRS and through clinical judgment of the CI, or who are likely to require hospitalization during the course of the study;
14. Have used “Ecstasy” (material represented as containing MDMA) at least once within twelve months of enrollment;
15. Require uninterrupted concomitant therapy with a psychiatric drug, including but not limited to SSRIs, SNRIs, or MAOIs;
16. Meet DSM-IV criteria for substance abuse or dependence for any substance in the past sixty days except caffeine or nicotine;
17. Have glaucoma, significant atherosclerosis, or hyperthyroidism;
18. Have any current problem, which in the opinion of the CI or Medical Monitor, might interfere with participation in the study;
19. Are participating in an interventional clinical trial concurrent with the study;
20. Are not able to give adequate informed consent.

## **5.0 Methods**

### **5.1 Measures**

The following outcome, safety, and process measures will be used in the study. All psychotherapy sessions, including experimental sessions, will be recorded to video, with all recordings preserved for research and training purposes.

#### **5.1.1 Outcome Measures**

The primary outcome measure will be the trait subscale of the State-Trait Anxiety Inventory (STAI), a 20-item self-report measure of intensity of anxiety [118]. The STAI is considered the definitive instrument for assessing anxiety in adults, and has been administered to advanced-stage cancer patients. Each item consists of a 4-point Likert rating scale ranging from 1 (‘Not at all’) to 4 (‘Very Much So’). The STAI differentiates between state anxiety, defined as anxiety experienced in reaction to a specific environmental circumstance, and trait anxiety, defined as long-standing nervous affect or anxiety disorder. The Trait score has good to strong test-retest reliability in adults and is a well-established measure of anxiety. The use of the trait subscale as the primary outcome measure is intended to target those anxiety symptoms that are chronic and pervasive. The STAI-Trait will be administered at baseline, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The secondary measure of anxiety symptoms will be the state subscale of the STAI (STAI-S), a 20-item self-report scale which will assess subjects' levels of transient, situationally oriented anxiety [118]. Like the trait subscale, participants respond to each item on the state subscale by selecting a response from a 4-point Likert scale. The comparison of the two subscales will provide information about the specific anxiolytic effects of MDMA, as well as the types of anxiety most often experienced in individuals with a life-threatening illness. The STAI-State will be administered at baseline, the third preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The Beck Depression Inventory-II (BDI-II) is a 1996 revision of the BDI, a 21-item self-report measure [119, 120], that will serve as a measure of depression according to DSM-IV criteria [121]. The BDI-II has been validated, has high internal consistency and good test/re-test reliability, and is not overly sensitive to daily variations in mood. It takes five to ten minutes to complete [121]. Score cutoffs indicate: 0-13 minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression. Higher scores indicate more severe depressive symptoms. The BDI-II will be administered at baseline, the third integrative session after the first experimental session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The Global Assessment of Function (GAF) is a measure of global functioning made through clinical observation. The GAF consists of a single score, with scores ranging from 0 to 100, with 100 reflecting superior function and zero reflecting serious risk of causing harm to the self or others. The GAF is a reliable, validated measure of social functioning [122]. The GAF will be administered by the blinded Independent Rater at the first preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The Pittsburgh Sleep Quality Index (PSQI) is a measure of self-reported sleep quality over a one month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers. It consists of 19 items, with possible responses ranging from zero to four on a five-point scale [123]. The PSQI consists of seven sub-scales; sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. These are all summed to produce a single global scale. Global scores can range from 0 to 21, with higher scores reflecting poorer sleep quality, and a score below 5 indicative of good sleep. It takes five to ten minutes to complete. Test-retest reliability ranges from 0.85 to 0.87, and it is internally consistent, with a Cronbach's alpha of 0.83 [123, 124]. Global scores correlate with other measures of alertness and self-reported sleep quality [125]. The PSQI will be administered at the first preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The Montgomery-Asberg Depression Rating Scale (MADRS) is a 10-item, clinician-administered questionnaire used to diagnose the severity of depressive episodes. The MADRS was designed as a measure of depression that would be more sensitive to the changes produced by treatment than previously existing scales [126]. Score cutoffs

indicate: 0-6 normal/symptom absent, 7-19 mild depression, 20-34 moderate depression, >34 severe depression. The MADRS will be administered by a blinded independent rater at the first preparatory session, the primary and secondary endpoint visits, and at the one, six, and 12-month follow-up visits. MADRS scores are strongly correlated with scores on the Hamilton Depression Rating scale [126].

The Posttraumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event [127]. It contains five subscales; relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life [127, 128]. In this study, subjects will complete the PTGI in reference to the time since their diagnosis at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions. Subjects will complete the PTGI according to the Time and Events table. The PTGI will be administered at the first preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits. The PTGI has been used in samples of people with life-threatening illnesses, such as diagnosis with breast cancer [129, 130].

The Posttraumatic Growth Inventory—Caregiver Form (PTGI-C) is a version of the original 21-item PTGI questionnaire containing the same items but with modified instructions for a caregiver to provide perceptions of subjects [131]. Where the subject version of the PTGI prompts the subject to answer based on their own experience, the PTGI-C prompts the caregiver or study partner to rate the study subject along the same metrics. This adaptation of the PTGI has not been validated, but has been used in other research, including studies of people with cancer or cancer survivors and significant others [130-132]. The PTGI-C will be administered at the first preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The Observer Rating Form is a 15-item questionnaire that prompts individuals close to the study subject to rate changes to the subject's mood, demeanor, and behavior over the course of their participation in the study. The ORF is typically administered to individuals who are in regular contact with the study subject. The ORF is not a peer-reviewed or validated scale, but it has been used in a currently ongoing study of psilocybin for anxiety associated with a life-threatening illness at Johns Hopkins University. The ORF will be administered to up to three individuals selected by the participant at baseline, the primary endpoint, and at the six- and 12-month follow-up visits. There are no current reports on validity or reliability of the ORF, but researchers investigating the effects of psilocybin have employed this measure [133].

The Functional Assessment of Chronic Illness Therapy Scale (FACIT-Sp) is a 27-item self-report measure of quality of life issues specifically relevant to individuals with a chronic or life-threatening illness or condition [134, 135]. The core questionnaire consists of four subscales: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. The version of the FACIT selected for this study also includes a 12-item spirituality subscale. The FACIT is a well-validated instrument with direct applicability to individuals with chronic health concerns. The FACIT will be

administered at the third preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The Death Attitudes Profile (DAP) is a 32-item self-report questionnaire that assesses individual attitudes and beliefs about death and dying. Each item on the scale is rated along a 7-point Likert scale ranging from ‘strongly agree’ to ‘strongly disagree.’ [136-138]. The DAP divides items along 5 dimensions: fear of death, death avoidance, neutral acceptance, approach acceptance, and escape acceptance. The DAP will be administered at the first preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The Five-Facet Mindfulness Questionnaire (FFMQ) is a 39-item self-report questionnaire that assesses how often and to what degree respondents experience or utilize mindfulness in their everyday life [139, 140]. Subjects respond to the FFMQ using a five-point Likert-type scale ranging from 1=never or very rarely true to 5=very often or always true. The questionnaire divides mindfulness into five component skills: observing, describing, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience. The FFMQ has been found to have good construct validity in discerning regular practitioners of mindfulness meditation from nonpractitioners [140-142]. Its use in this study is intended to explore the effects of MDMA-assisted psychotherapy on experiences of mindfulness, regardless of past meditation or mindfulness experience. The FFMQ will be administered at the second preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits.

The Self-Compassion Scale (SCS) is a 26-item self-report questionnaire that assesses how respondents relate to themselves and treat themselves during difficult or painful experiences [143]. Items are scored along a 5-point Likert-type scale ranging from 1=almost never to 5=almost always. The SCS has six component scores: self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identification. These subscores can also be used to generate an overall composite score. Higher scores have been found to correlate with positive mental health outcomes, as well as decreased depression and anxiety. The SCS will be administered at the second preparatory session, the primary and secondary endpoints, and at the one, six, and 12-month follow-up visits. The SCS is reliable, with strong test-retest reliability and validation in comparison with measures selected for similarity or distinctness from the construct [143]

The Long-term Follow-up Questionnaire has been developed internally by the sponsor to assess long-term benefits and harms of MDMA-assisted psychotherapy at the six and 12-month follow-up visits. The measure has been used to assess the durability and nature of effects of MDMA-assisted psychotherapy in people with PTSD [2].

### **5.1.2 Safety Measures**

Safety measures will be applied, as described below, to minimize risks associated with drug-assisted psychotherapy sessions. The therapists will be available via mobile phone

or pager throughout the study to ensure subject safety. The therapists will maintain Basic Life Support (BLS) certification.

Safety measures, including vital signs and a measurement of psychological distress, will be assessed during all experimental sessions. Subjects will rate their current degree of subjective distress with the SUD scale, which is a single-item self-report scale. The SUD will be completed repeatedly during the experimental sessions, with the degree of distress described as a single number along a seven-point scale. Results of the SUD are intended to assist therapists in maintaining subject safety during Experimental sessions.

The therapists will assess general wellbeing during each preparatory session, on each integrative session and during integrative telephone calls for seven days. Results of this scale are intended to assist therapists in maintaining subject safety throughout the study.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [144]. It consists of a Baseline form that assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation and behavior. The C-SSRS consists of a series of questions, and can be administered during a face-to-face interview or over the telephone. Suicidality will be assessed at Baseline, once during any face-to-face visit, during the second and seventh days of integrative telephone contact, and twice during each experimental session. Subjects who are discontinuing medication to participate in the study will complete the C-SSRS before and after medication washout. The C-SSRS data will be collected on Case Report Forms (CRFs) for all administrations except for the second integrative session, unless the therapists observe an increase in suicidality. C-SSRS data from the second integrative session after each experimental session will be kept with the subject's Source Record.

The Brief Pain Inventory—Short Form (BPI-S) is a self-report measure of physical pain symptoms that is intended to provide an overall picture of subjects' chronic pain over the course of the study [145]. The BPI-S includes a visual component, where subjects are asked to indicate where on their body they experience pain, scales for rating pain severity, efficacy of pharmacotherapy in relieving pain, and the degree to which pain impinges upon subjects' ability to function. This measure or translations of it are used in studies assessing cancer pain and pain arising from other illnesses, such as osteoarthritis [7, 146, 147] The BPI-S will be administered during the preparatory period, as well as at the first integrative session following each experimental session, and at the primary and secondary endpoints.

Cardiovascular effects will be assessed via blood pressure and pulse measurement. Blood pressure and heart rate will be assessed periodically during each experimental session by an automatic blood pressure (BP) and pulse monitor. Blood pressure and pulse will be measured at the outset of the experimental session, once approximately every 30 minutes for the first four hours of the experimental session, and then once every hour, or as needed, thereafter. More frequent measures will be taken if the established thresholds of 180 systolic, 120 diastolic, or pulse of 120 are exceeded. Blood pressure will also be

measured more frequently if there are symptoms, such as chest pain, shortness of breath, or neurological symptoms that may be indicative of hypertension. The therapists will measure subject body temperature approximately every 60 to 90 minutes. Cardiovascular effects will be assessed via blood pressure measurement. The timing of these measurements will be adjusted so that they do not interfere with the therapeutic process.

All AEs and spontaneously reported reactions will be collected, as described in Section 8.5. AEs and spontaneously reported reactions may be collected during face-to-face visits or over the telephone. Common reactions that are spontaneously reported are collected for seven days after each experimental session on a separate CRF page and will be categorized as mild, moderate, or severe.

### **5.1.3 Process Measures**

All psychotherapy sessions, including experimental sessions, will be recorded to audio and video, with all recordings preserved for research and training purposes.

Belief of condition assignment and certainty will be collected from each therapist responsible for treating the subject and the subject at the integrative session on the day after each blinded experimental session in Stage 1. These beliefs are collected as a part of the sponsor's ongoing initiative to optimize the double-blind as a part of dose response studies.

The States of Consciousness Questionnaire (SOCQ) is a 100-item questionnaire based on the "Peak Experience Profile" designed by Pahnke and colleagues [133, 148]. Subjects respond to the SOCQ using a six-point Likert-type scale anchored at 0=none at all and 5=extreme (more than ever before in my life). It has seven subscale scores; internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. The measure is a self-report instrument and takes approximately twenty to thirty minutes to complete. Subjects will complete the SOCQ after each experimental session, at any time between the end of an experimental session and prior to leaving the treatment facility the next day.

The Psychological Process Questionnaire (PPQ) is a 35-item companion questionnaire to the SOCQ designed by investigators working with the SOCQ, in which subjects rate each item along the same six-point Likert-type scale. It is intended to capture a broader array of experiences and benefits than those captured in the SOCQ, particularly in respect to perceived insights or benefits from alterations in consciousness [149]. The PPQ focuses primarily upon changes in cognitive and/or emotional processing that may be experienced in the course of an MDMA-assisted psychotherapy session, and is intended to provide a fuller picture of the changes in perception that may occur during treatment sessions. Subjects will complete the PPQ after each experimental session, at any time between the end of an experimental session and prior to leaving the treatment facility the next day.

## **5.2 Study Procedures and Visit Descriptions**

### **5.2.1 Prescreening, Screening, and Baseline Evaluation - Pre-study**

Prospective subjects will be prescreened by telephone according to an IRB-approved script to learn if they meet basic eligibility criteria. This script will include the STAI-Trait and the Overall Anxiety Severity and Impairment Scale (OASIS) [150] instruments as a means of estimating eligibility for the study. Data from these assessments will not be used in any study analyses, and the STAI-Trait assessment will be repeated in full at each subjects' baseline visit. All individuals who are prescreened should be assigned a screening number and recorded on the Subject Screening Log where information on the selection of potential subjects in the trial should be collected.

Upon signing the IRB-approved informed consent form (ICF), the potential subject may commence study-related screening activities. The screening number should also be recorded on the signed ICF. If a subject is enrolled, the study staff should record the enrollment date and assign a subject number. If a subject is not enrolled, an explanation should be recorded on the Screening Log. A CRF will not be completed for subjects who are not enrolled. These subjects will only be documented on the Screening Log and Source Records. It is the responsibility of the CI to file the Screening Log in the investigator site file (ISF) to be readily available for on-site monitoring and/or inspection by relevant authorities. Screening may take place over more than one day and should be complete by up to two months prior to enrollment. If, after reviewing all information, the CI concludes that a subject is eligible, they will enroll the subject in the study. Visits will be scheduled consecutively, as described in the Time and Events Table.

- a. Explain and obtain written informed consent from the subject. Written informed consent must be obtained prior to performing any tests or evaluations for the study. Any potential subjects who are private patients of the CI must have their records and eligibility reviewed by an independent physician, who will also conduct the informed consent process with the subject.
- b. Assign the subject a screening number. Complete the Screening Log.
- c. Review the ability of females of childbearing potential to become pregnant and their commitment to practice appropriate birth control, as determined by the CI for the treatment period of the study.
- d. The PI will obtain medical and psychological history by interview.
- e. The PI will collect information on pre-study and current medications.
- f. The PI will perform a general physical examination. The examination will involve the following procedures:
  - Blood pressure
  - Pulse
  - Height

- Weight
- Body temperature
- Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen, and extremities
- Brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes, and cerebellar function)
- Electrocardiogram (ECG)
- Serum electrolytes, metabolic profile, urinalysis, and complete blood count
- Thyroid stimulating hormone (TSH), free T3, and free T4
- Human Immunodeficiency Virus (HIV) serology
- Urine-dip pregnancy test on females with childbearing potential
- Urinary drug test
- C-SSRS to assess suicide risk

Results of HIV serology will be kept confidential and appropriate referral for counseling may be necessary in accordance with state law. The clinical laboratory values will be used to establish eligibility and will be kept with the subject's Source Record. The clinical laboratory values will not be captured in the CRF, but will be used to establish eligibility and will be kept with the subject's Source Record. Clinically significant abnormal values will be captured as medical history. If, upon examination, there are questions raised about possible medical problems, the PI will request a review of subject medical records and request additional tests or assessments, as indicated.

The PI, or another qualified investigator will administer:

- Structured Clinical Interview for DSM-IV Research Version (SCID-RV) to assess eligibility based on DSM-IV diagnoses, which includes a self-report questionnaire to focus on modules to use based on symptoms.

The subject will complete the following self-report measures:

- STAI to assess anxiety symptoms, and to determine eligibility
- BDI-II to assess depression symptoms

### **5.2.2 Preparatory Psychotherapy Sessions - Visits 1, 2, 3 (Stage 1), 18 (Stage 2)**

Subjects who do not complete all screening activities will not be enrolled. Eligibility may be discussed by phone after screening is complete and at the time Visit 1 is scheduled but the final confirmation will occur at Visit 1. If all inclusion criteria and no exclusion criteria are met, eligibility will be confirmed with the subject.

- a. Complete a final review of inclusion/exclusion criteria.
- b. Assess general wellbeing.
- c. Confirm eligibility and willingness to participate in study.
- d. Enroll subject and issue subject number.
- e. Ensure medical history and medication history is complete. After enrollment new events will be collected as AEs and new medications, as described in Section 8.5 and Section 9.0.

- f. Discuss medication tapering, if applicable. Upon confirmation of eligibility, the PI will consult the prescribing physician to initiate medication tapering for subjects who must refrain from taking a psychiatric medication during the study period, beginning with enrollment through the one-month follow-up visit following the subject's final experimental session. Tapering will follow a time course appropriate for the medication given its half-life, with the first experimental session scheduled to occur after complete washout.

The subjects will undergo three preparatory sessions lasting approximately ninety minutes with their therapist team, prior to their first experimental session. The first preparatory session will take place at Visit 1 after enrollment confirmation. In Stage 2 (for placebo crossover subjects) only one preparatory session will take place prior to their first active dose open-label experimental session, as described in the Time and Events Table.

During the preparatory sessions:

- a. Therapists will record all sessions to audio and video. Subjects may receive copies of audio or video recordings from these sessions upon request.
- b. Collect AEs and Medications, as described in Section 8.5 and Section 9.0.
- c. The therapists will inquire about any possible changes in the subject's health to ensure that subject continues to meet eligibility criteria and, if applicable, will confirm that the subject has appropriately tapered off of medications.
- d. The subject and therapists will discuss goals for the experimental session and will review what will happen during the experimental session.
- e. If a subject would like a companion present during or after the experimental session, a meeting between the therapists and that individual will be scheduled prior to the first experimental session. There must be mutual agreement between the subject and therapists concerning the presence of the companion. The companion can be but is not required to be the caregiver, transportation partner, or one of the observers.
- f. The blinded Independent Rater will administer the GAF and MADRS at the first preparatory session.
- g. The subject will complete the DAP, PTGI, and PSQI at the first preparatory session.
- h. The subject's caregiver will complete the PTGI-C at the first preparatory session.
- i. Up to three individuals in close contact with the subject will complete the ORF during the preparatory period, prior to the first experimental session. One of them may be the caregiver, transportation partner, and/or experimental session companion.
- j. The subject will complete the FFMQ and SCS at the second preparatory session.
- k. The subject will complete the FACIT, STAI-State, and BPI-S at the third preparatory session.
- l. The therapists will administer the C-SSRS just prior to beginning the second preparatory session, unless a subject is still undergoing medication washout. Subjects still undergoing medication washout will complete the C-SSRS during the second preparatory session or at a point after washout is complete prior to the first experimental session.

- m. Assess general wellbeing at each preparatory session.
- n. During the third and last preparatory session, give the Reminder of Study Rules to the subject, which includes instructions and restrictions for conduct prior to receiving the drug. Subjects must agree to:
  - Ingest only alcohol-free liquids after 24:00 (midnight) the evening before the experimental session.
  - Refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session.
  - Not use caffeine or nicotine for two hours before and six hours after ingesting the drug, or until therapists deem it safe to do so.

### 5.2.3 Experimental sessions - Visits 4, 8 (Stage 1), 13, (Active dose Group Stage 1), 19, 23, 28 (Stage 2)

Subjects in Stage 1 will receive two experimental sessions of MDMA-assisted psychotherapy, blinded with respect to dose, scheduled approximately two to four weeks apart. Subjects in the open-label third experimental session in Stage 1 and open-label Stage 2 will receive experimental sessions with the active dose of MDMA. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions and all procedures except the dose of the drug received will be the same.

Generally, therapists will create and communicate a setting of safety and support the subject during periods of inner focus. Therapists will use a largely nondirective approach, following the lead of the subject's inner healing intelligence. Therapists will provide encouragement for staying present with difficult experiences. Therapists may occasionally offer gentle guidance or redirection as a choice to encourage collaborative exploration if the subject repeatedly avoids relevant material. Therapists will inquire about somatic symptoms and if necessary encourage release of tension through movement, in whatever way feels appropriate to the subject. Therapists will use music to support the experience without being intrusive.

The Principal Investigator will monitor all experimental sessions for medical issues in his capacity as a licensed physician. If the PI is the treating therapist for a subject, he will conduct this monitoring concomitant to the session therapy. If the subject is being treated by another therapist team, the PI will be available to supervise the session via closed-circuit camera system from an adjacent room.

**Table 4. Schedule of Procedures for Experimental Sessions**

Approximate Time	Procedure or Action
9:00	Urine drug screen and pregnancy test. Subject acclimated to environment, C-SSRS
9:45	Baseline Blood Pressure (BP), Pulse, Subjective Units of Distress Rating (SUD)
9:55	2 <sup>nd</sup> Baseline BP, Pulse, Body Temperature (BT), SUD
10:00	<b>MDMA Administration</b> , begin recording to audio and video

10:30	BP, Pulse
11:00	BP, Pulse, SUD, BT
11:30	BP, Pulse; <b>Administer optional Supplemental Dose</b>
12:00	BP, Pulse, BT
12:30	BP, Pulse, SUD
13:00	BP, Pulse
13:30	BP, Pulse, BT
14:00	BP, Pulse, SUD
Every hour and as needed	BP, Pulse
Every sixty to ninety minutes	SUD, BT
Approximately six hours after drug administration	C-SSRS, General Wellbeing

Pre-drug:

- At least 24 hours prior to the first experimental session the subject will be randomized to one of the two conditions. The PI will obtain the container assignment using a web-based randomization program prior to the blinded sessions.
- On the day of the experimental session, the subject will arrive approximately one to one and a half hours prior to drug administration.
- Confirm continuing eligibility by reviewing inclusion/exclusion criteria.
- Perform a urine drug screen. A positive drug screen will be reviewed by the CI and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the subject from the study.
- If a woman is of childbearing potential, perform a urine pregnancy test. A positive pregnancy screen is cause for withdrawal from the protocol.
- If the subject continues to meet criteria and the subject reports that they followed appropriate rules and restrictions, the session will proceed.
- Review procedures for the experimental session with the subject.
- Record the entire session to video and audio. Subjects may review video recordings of their experimental sessions upon request.
- The session will last for approximately eight hours or longer, followed by an overnight stay at the study site.
- The therapists will administer the C-SSRS prior to drug administration.
- Before drug administration, discuss and review the subject's goals, intentions, and concerns and some of the commonly experienced effects of MDMA.
- Instruct the subject not to use caffeine or nicotine two hours before or six hours after the dose of drug.
- Subject body temperature will be measured at baseline prior to administration of the initial dose and approximately every hour after that. The therapists may make more frequent measurements if body temperature exceeds more than 1°C above baseline.
- Subjects will complete the SUD at baseline prior to administration of the initial dose. Subjects will complete the SUD every 60 to 90 minutes, until the session is over,

allowing a window of up to 30 minutes to fit into the psychotherapy process where a natural break occurs. If necessary, the therapists can make a greater number of measurements, as their clinical judgment dictates.

- o. Measure blood pressure and pulse at baseline prior to the experimental session and once every half-hour for the first four hours of the experimental session, and once every hour thereafter if the established thresholds for normal blood pressure and pulse have not been exceeded for the duration of the experimental session. More frequent measures will be taken if the established thresholds of 180 systolic, 120 diastolic, or pulse 120 are exceeded. Measurements should be taken more frequently until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the CI to be safe. The therapists may also make more frequent measurements if a subject exhibits symptoms indicative of hypertension.

During:

- p. At approximately 10:00 in the morning, subjects will receive the initial dose of drug along with a glass of water.
- q. The subject will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided if the subject wishes to use them. Subjects may speak to the therapists whenever they wish, who will provide guidance and support, as needed.
- r. After the first hour, if the subject has not spoken spontaneously, check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapists will support and encourage the subject in emotional processing and resolution of whatever psychological material is emerging.
- s. Record any spontaneously reported reactions during the session.
- t. Provide water and electrolyte containing fluids throughout the session but not to exceed 3 L overall.
- u. A supplemental dose half the size of the initial dose will be administered approximately one and a half to two and a half hours after the initial dose, unless contraindicated.
- v. Provide food during the latter part of the session.
- w. If there is a companion who has previously been asked and has agreed to be present during part or all of the MDMA session, that person may arrive during the session at whatever time has been agreed upon, but will wait in the waiting room until brought back to the session room by one of the therapists. Alternatively, the support person may arrive after the session has ended.
- x. If it is appropriate to do so, initiate the first question of the C-SSRS at any point in the session if the subject is experiencing significant psychological distress that does not respond readily to processing with the therapists. The C-SSRS is required at least once during the session. It is preferable to administer it towards the end of the session, about six hours after the initial dose.
- y. End the session if all medical and psychiatric parameters are acceptable and the subject is alert, ambulatory, and emotionally stable.

Post-drug:

- z. Give the subject the SOCQ and PPQ to be completed after the end of the experimental session and prior to leaving the treatment facility the next day.
- aa. The therapists will depart the site when they have concluded that the subject is emotionally and medically stable. Therapists or the PI shall remain available to subjects during the experimental session and for one week after via 24 hour cellular phone for integration, as needed.
- bb. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.

Subjects will remain overnight in an appropriately furnished room at the study site. With the approval of the therapists, a companion may accompany the subject during the overnight stay. An attendant will check in periodically on the subject during the overnight stay, even if a companion is present. The attendant will monitor subject condition and will help subjects relax during the overnight stay. The attendant will be an individual with some previous training in managing psychological distress. If there is an emergency or the subject needs additional support, the attendant can contact the therapists. The subject and a companion (if applicable) will receive information that will allow them to contact the therapists during the overnight stay in the case of an emergency or request for additional support. Subjects will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

#### **5.2.4 Integrative Sessions 24 Hours after Experimental Session - Visits 5, 9 (Stage 1), 14 (Active dose Group Stage 1), 20, 24, 29 (Stage 2)**

On the morning after each experimental session, both of the therapists from the subject's team will meet with the subject during a 60 to 90 minute integrative psychotherapy session.

Generally, these sessions include discussing material that emerged during experimental sessions and helping subjects integrate their experiences both internally and into daily life. Therapists will validate the choices of the subject about how much they wish to communicate their thoughts, feelings, and experiences at this time, but will elicit enough information to be able to assess the subject's level of emotional stability and state of emotional and physical wellbeing. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone for additional meetings if needed. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

During integrative sessions:

- a. The integrative session will be recorded to audio and video. Subjects may receive copies of this session upon request.
- b. The therapists will administer the C-SSRS during each integrative session.
- c. If applicable, subjects will complete the BPI-S at the first integrative session

- immediately following each experimental session.
- d. Prior to the integrative session, the subject and both therapists will indicate their beliefs concerning subject condition assignment.
  - e. Discuss and review events that occurred with the subject during the experimental session, including thoughts, feelings, and memories. If necessary, the therapists will help the subject to reduce any residual psychological distress he or she is experiencing. The therapists will also encourage the transfer of states of acceptance, feelings of intimacy, closeness, and reduced fear experienced in experimental sessions to emotionally threatening everyday situations. The therapists will be supportive, validating the experience, and facilitating understanding and emotional clearing.
  - f. The therapists will remain accessible any time the subject needs support outside the scheduled integration sessions.
  - g. Assess the subject's mental health and the presence of any remaining reactions during the integrative session.
  - h. Integrative sessions can also serve as an opportunity for the therapists to gather information about the effects of the drug on the subject in an unstructured manner.
  - i. After the integrative session, a person previously selected by the subject will provide a ride home to the subject. If the subject is unable to locate an individual willing or able to take him or her home, or if the designated person is unable to assist the subject due to unforeseen events, the therapists will assist the subject in finding an alternative means of returning home.
  - j. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.
  - k. Remind the subjects that they will have daily phone contact for the next seven days.

#### **5.2.5 Daily Telephone Contact for Seven Days after an Experimental Session**

During daily phone contact:

- a. Starting on the day of the integrative session following each experimental session, one of the therapists will contact the subject via telephone or in person on a daily basis for one week. The goal of daily contact is assessment of changes in general wellbeing, safety of the subjects, and offering support for subjects.
- b. The integrative phone contact will be for a brief check-in lasting five to fifteen minutes or as long as necessary to address any subject's concerns and to assess subject's wellbeing. Additional telephone contact can be initiated at the request of the therapists or subject.
- c. On the second and seventh day of contact after the experimental session, one of the therapists will administer the C-SSRS.
- d. General wellbeing will be assessed at each phone call.
- e. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.

### **5.2.6 Integrative Sessions between Experimental sessions - Visits 6, 7, 10, 11 (Stage 1), 15, 16 (Active dose Group Stage 1), 21, 22, 25, 26, 30, 31 (Stage 2)**

In addition to the integrative session the morning after each experimental session, the subject will have two additional integrative sessions with the therapists lasting 60 to 90 minutes with the therapists between each experimental session and in the month following the last experimental session. The therapists may conduct more integrative sessions if they and the subject deem it necessary.

Generally, these sessions include integration of material that emerged as a part of experimental sessions and afterward into daily life. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone or pager. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

During integrative sessions:

- a. Record each integrative session to audio and video. Subjects may review video of one or more integrative sessions upon request.
- b. The C-SSRS will be administered just prior to beginning each integrative session.
- c. General wellbeing will be assessed at each integrative session.
- d. The subject will complete the BDI-II at the third integrative session following the first experimental session only, according to the Time and Events Table.
- e. The subject and therapists will continue to work on supporting the subject as she or he considers his or her experiences during experimental sessions.
- f. The therapists will use clinical judgment to assess the subject's psychological wellbeing during this period of time. If there are any indications of continuing anxiety or distress, the therapists may arrange to work on reducing the distress at a specially scheduled integrative session, through continuing contact, or at the next regularly scheduled integrative session. The subject may also initiate contact with the therapists at any time throughout the study.
- g. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.
- h. NOTE: If an integrative session falls within the period of telephone contact and additional phone call is not required that day, all data normally collected during the telephone call will be completed in person.

### **5.2.7 Evaluation at Primary Endpoint and Unblinding - Visit 12 (Stage 1)**

The Primary Endpoint evaluation in Stage 1 will occur one month (within a window of +/- one week) after the second blinded experimental session. This visit will consist of two meetings that may be completed on separate days, one with the IR and the other with the therapists. Subjects who have withdrawn from treatment but have continued for follow-up will also complete this time point one month after their last experimental session.

At the Primary Endpoint:

- a. The blinded IR will administer:
  - MADRS to assess depression symptoms
  - GAF to assess general psychological function
- b. The subject's support partner will complete the PTGI-C
- c. The individuals who completed the ORF at baseline will repeat the assessment.
- d. The subject will complete the following self-report measures:
  - STAI to assess anxiety symptoms
  - BDI-II to assess depression symptoms
  - DAP to assess changes in attitudes toward death
  - PTGI to assess posttraumatic growth
  - PSQI to assess sleep quality
  - FFMQ to assess mindfulness
  - SCS to assess self-compassion
  - FACIT to assess quality of life/care
- e. After completing all assessments and measures with the IR, the subject will meet with the therapists for approximately 30 minutes.
- f. The therapists will assess suicidality with the C-SSRS.
- g. General wellbeing will be assessed.
- h. The blind will be broken for the subject's condition assignment. Only the IR will remain blind to condition assignment at this time.
- i. If the subject was assigned to receive placebo, the therapists will discuss enrollment in Stage 2 (See Section 5.2.9). Subjects receiving placebo will not complete the third experimental session and associated integrative sessions in Stage 1.
- j. If the subject was assigned to receive active dose MDMA, the subject will complete a third open-label experimental session, with associated daily phone calls and integrative sessions in Stage 1 (See Section 5.2.3, Section 5.2.4, Section 5.2.5, and Section 5.2.6).

### **5.2.8 End of Stage 1 - Visit 17 (Active dose Group Stage 1)**

Subjects receiving active dose MDMA will repeat all outcome measures with the IR and meet with the therapists again one month (within a window of +/- one week) after their final open-label experimental session, which will be their final visit in Stage 1 (See Section 5.2.7). This visit will consist of two meetings that may be completed on separate days, one with the IR and the other with the therapists. A qualitative, semi-structured interview will be conducted by one of the therapists, which will provide narrative data about subjects' experiences in the study.

At the End of Stage 1:

- a. Subjects receiving active dose MDMA who complete Stage 1 and subjects receiving placebo dose MDMA who elect not to participate in Stage 2 will continue on to the long-term follow-up visit.
- b. Subjects who will continue on to the long-term follow-up may return to taking psychiatric medications after the End of Stage 1 if necessary.
- c. Subjects who will continue on to the long-term follow-up will receive a memory aid card for use between their End of Stage 1 visit and the twelve-month follow-up. Subjects will use this card to record AEs, medications, and changes in psychiatric status that they will be asked about at the termination visit. Memory Aids will not be collected.
- d. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.

### **5.2.9 Open-Label Stage 2 (Placebo Group from Stage 1)**

During Stage 2:

- a. Subjects will be reminded that participation in Stage 2 is voluntary and optional.
- b. Subjects who elect to cross over to Stage 2 will undergo the same course of therapy and evaluation as in Stage 1, but with active dose MDMA during three experimental sessions.
- c. Assessment of PTSD symptoms at the Primary Endpoint will serve as baseline assessments in Stage 2.
- d. If the start of Stage 2 is delayed for more than thirty days from the Primary Endpoint (Visit 12) to the first preparatory session in Stage 2 (Visit 18), the IR will re-administer the MADRS and GAF, and the subject will complete the STAI, DAP, PTGI, PTGI-C, PSQI, BDI-II, FFMQ, SCS, and FACIT, and these scores will be used as the baseline for comparison to assessment at the Secondary Endpoint and the End of Stage 2.
- e. Subjects entering Stage 2 will meet with both therapists for a single preparatory psychotherapy session.
- f. Subjects will have the same sequence of Experimental sessions and integrative sessions as subjects receiving active dose MDMA in Stage 1 in an open-label context (e.g. without unblinding). Visits will be scheduled consecutively according to the Time and Events Table.
- g. The same outcome measures completed by subjects receiving active dose MDMA in Stage 1 will be administered during Stage 2.
- h. The same safety measures as those in Stage 1 will be administered during Stage 2.
- i. The End of Stage 2 will be completed in the same manner as the End of Stage 1 (See Section 5.2.8).

### **5.2.10 Long-term Follow-up**

All subjects will be evaluated for long-term effects six and twelve months (within a visit window of +/- 1 month) after their last MDMA-assisted psychotherapy session. These

visits will consist of two meetings, one with the IR and the other with the therapists. Subjects who have withdrawn from treatment but have continued for follow-up will also complete this time point whenever possible.

At the long-term follow-up visit:

- a. The IR will administer the MADRS and GAF.
- b. Subjects will complete the STAI, DAP, PTGI, PTGI-C, PSQI, BDI-II, FFMQ, SCS, and FACIT.
- c. The subject's support partner will complete the PTGI-C.
- d. The individuals who completed the ORF at baseline and the primary endpoint will repeat the assessment.
- e. Subjects will have a final meeting with at least one of the therapists to review specified AEs and medications since the last visit. Subjects should bring the Memory Aid Cards to this visit, to be used as aids in recollection. These cards will not be collected. AEs and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.
- f. One of the therapists will assess suicidality with the C-SSRS.
- g. General wellbeing will be assessed.
- h. Subjects will complete a questionnaire assessing positive and negative long-term effects of the study.
- i. Subjects will complete the termination visit at this time.

### **5.3 Randomization and Subject Numbering**

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "S001". Subjects who meet all inclusion criteria and no exclusion criteria will be enrolled into the study and will be assigned a five-digit alphanumeric subject identification number. The first two digits will be "51" and will identify the protocol. The next three digits identify the subject within the site and will be assigned sequentially, with 001 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 51001, the second will be 51002, etc.

In total, 18 subjects will be enrolled into the study. The randomized portion of the study will be blinded and there will be a 13:5 ratio between subjects in the active dose and placebo conditions. An unblinded Randomization Monitor will generate the randomization list. Subjects will be assigned subject numbers consecutively, and subjects will be randomized in a blinded fashion. Upon enrolling a subject, the CI will be provided with an enrollment code for that subject. Randomization numbers will be pre-printed on the container labels corresponding to doses for individual sessions. Randomization will be performed at least 24 hours before the experimental session for each subject. The therapists will utilize a web-based randomization program to obtain the container assignment for each experimental session. Blinded personnel will conduct all study evaluations in the randomized portion of the study until the blind is broken for each

subject at the Primary Endpoint per protocol via the web-based randomization program. Detailed instructions will be provided to the site in a separate document.

If there is an emergency requiring knowledge of subject's condition assignment, the blind may be broken for an individual subject. The CI will be provided with sealed emergency unblinding envelopes corresponding to each enrollment code. These sealed envelopes will be stored in a secure limited access area and should remain sealed if there are no emergency unblinding events during the study.

#### **5.4 Removal of Subjects from the Study**

Subjects can withdraw consent at any time without prejudice. The therapists can withdraw a subject if, in their clinical judgment, it is in the best interest of the subject or if the subject cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study. If the therapists withdraw a subject from the study, the therapists will explain the reason for withdrawing the subject. The reason for early termination will be recorded in the subject's Source Records and CRF.

Subjects will be clinically monitored after withdrawal, the cause of which will be recorded in the subject's source records and CRF. Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the PI and/or sponsor.

If a subject develops any exclusion criteria that in the opinion of the Medical Monitor, affects the safety of the subject, including psychiatric diagnosis, pregnancy, or requiring use of excluded medications, the subject will discontinue treatment but remain in the study for follow-up purposes. Whenever possible, the tests and evaluations listed for the Primary Endpoint and twelve-month follow-up will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the PI, Medical Monitor, and/or sponsor.

Subjects who discontinue treatment prior to the second experimental session will be replaced. Individuals who replace these subjects will be assigned the next available subject number. Subjects who discontinue treatment after the second experimental session will not be replaced. If Stage 1 subjects discontinue treatment before the second experimental session, the site should contact the Randomization Monitor for replacement instructions. Detailed instructions will be provided to the site in a separate document.

#### **5.5 Premature Discontinuation of the Study**

The sponsor or the PI (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the CI is to promptly inform the study subjects and will assure appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be

returned to the sponsor and will be treated in accordance with federal and state regulations.

## 6.0 Investigational Product

### 6.1 Description of Active Compounds

The investigational product to be used in this protocol is MDMA. This ring-substituted phenethylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor [151-153]. Its direct actions on serotonergic, adrenergic and other receptors are considerably lower. See Section 2.2.3 and the IB for more information on the investigational product.

### 6.2 Preparation and Administration

In this study, 18 subjects will be randomized to the two conditions, as described in Table 5 (below). The blind will be broken for each subject after the Primary Endpoint is completed. The subjects who received MDMA will be offered one additional open-label experimental session with active dose MDMA. The subjects who received the placebo will be offered the opportunity to enroll in an open-label Stage 2 where they will receive active dose MDMA-assisted psychotherapy. Stage 2 visits will be conducted in a manner similar to Stage 1.

#### 6.2.1 Doses

**Table 5. Doses of MDMA**

Number of Subjects	Condition (first 2 exp. Sessions)	Blind?	Initial Dose	Supplemental Dose	Cumulative Dose
5	Placebo	Blinded	0 mg	0 mg	0 mg
13	Active dose	Blinded	125 mg	62.5 mg	187.5 mg
5	Active dose	Stage 2 Open Label	125 mg	62.5 mg	187.5 mg

#### 6.2.2 Compounding and Encapsulation

MDMA in bulk will be sent from a Schedule 1 licensed storage facility to the Drug Enforcement Agency (DEA) Schedule I license holder for the study. The Schedule I license holder and unblinded randomization monitor will oversee compounding by a pharmacist in a manner that will maintain the blind for the Schedule I license holder. The pharmacist will provide bulk lactose for compounding MDMA capsules. The pharmacist will compound the MDMA with lactose into doses of 125 mg and 62.5 mg (calculated as the weight of the hydrochloride salt) and placed in gelatin capsules. Capsules for the initial dose will be clearly differentiated from capsules used for the supplemental dose by individually labeled packages. All capsules will be compounded so that they weigh the same amount, but contain varying amounts of MDMA and lactose.

The encapsulation will be performed by a pharmacist who has the appropriate skills. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose used to ensure that all capsules have similar appearance and weight. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent Clinical Investigators and subjects from distinguishing contents of active dose and comparator dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging.

### 6.2.3 Labeling

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with federal and state regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled “inner envelopes” within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.

**Figure 2. Holding Box Label**

Box Label
MAPS Study: MDA-1
Investigational Product: MDMA OR PLACEBO
Dose: 0mg OR 125 mg OR 62.5 mg Lot #: XXXXX
Administer as per Protocol
Caution: Limited by Law to Investigational Use Only

### Figure 3. Container Labels

#### Stage 1 Primary Container Labels

##### Blinded Sessions

Container Label MAPS Study: MDA-1  
**Stage 1**  
Lot #: XXXXX  
Container #: XXX  
  
Subject #: \_\_\_\_\_  
Exp. Session #: \_\_\_\_\_  
  
Administer as per Protocol  
Investigational Use Only

##### Open-Label Session 3

Container Label MAPS Study: MDA-1  
**Stage 1 – Open Label**  
Lot #: XXXXX  
Container #: XXX  
125 mg & 62.5 mg MDMA  
  
Subject #: \_\_\_\_\_  
Exp. Session #: 3  
  
Administer as per Protocol  
Investigational Use Only

#### Stage 1 Inner Envelope Labels

##### Blinded

Stage 1 Container # XXX  
INITIAL DOSE  
Subject # \_\_\_\_\_ Ex. Ses # \_\_\_\_\_

##### Blinded

Stage 1 Container # XXX  
SUPPLEMENTAL DOSE  
Subject # \_\_\_\_\_ Ex. Ses # \_\_\_\_\_

##### Open Label Session 3

Stage 1 Container #XXX  
INITIAL DOSE 125mg  
Subject # \_\_\_\_\_ Ex. Ses # \_\_\_\_\_

##### Open Label Session 3

Stage 1 Container #XXX  
SUPPLEMENTAL DOSE 62.5mg  
Subject # \_\_\_\_\_ Ex. Ses # \_\_\_\_\_

#### Stage 2 Primary Container Labels

Container Label – MAPS Study # MP-12  
**Stage 2**  
125mg & 62.5mg MDMA  
Lot # XXX  
Container # **XXX**  
  
Subject # \_\_\_\_\_  
Exp. Session # \_\_\_\_\_  
Administer as per protocol Investigational Use Only

#### Stage 2 Inner Envelope Labels

Stage 2 Container#XXX  
INITIAL DOSE 125mg  
Subject # \_\_\_\_\_ Exp. Ses # \_\_\_\_\_

Stage 2 Container#XXX  
SUPPLEMENTAL DOSE 62.5mg  
Subject # \_\_\_\_\_ Exp. Ses # \_\_\_\_\_

Each dose will consist of the specified amount of racemic MDMA mixed with an inactive substance, such as lactose, to prevent the therapists from distinguishing doses through weight or appearance of the capsules. Initial doses will be distinguished from supplemental doses through labeling them to ensure that the correct dose is administered at the scheduled time. Each dose of MDMA will be administered along with a glass of water or electrolyte-containing fluid. MDMA will be administered in the same manner during each experimental session.

### **6.3 Drug Accountability**

Forms will be provided to track drug accountability and administration throughout the study. Blinded drug accountability and administration logs will be reviewed during routine monitoring visits. MDMA will be handled in accordance with all state and federal regulations and forms pertaining to the use of controlled substances, and forms will be maintained by the Schedule 1 License Holder.

Each primary container label will contain a unique container number for the drug assigned to a single experimental session. The container numbers will be used to track drug administration in the Source Record and the drug administration log. The web-based randomization system will enable tracking of blinded primary containers for drug accountability purposes.

### **6.4 Drug Storage and Handling**

MDMA is a Schedule I compound and will be stored and handled in compliance with all relevant federal and state regulations. In accordance with these requirements, the Schedule I license holder will be responsible for storing, dispensing, and administering the MDMA. It will be stored in a secure safe in accordance with federal and state regulations.

IP will only be removed for a single experimental session at a time and will be administered orally at the office of the PI. All doses administered will be recorded on the appropriate accountability and administration logs. Only the initial dose is required to be given at each experimental session. Supplemental doses are provided for each experimental session but are optional to use.

The Schedule 1 License Holder will dispense the appropriate container number for each experimental session. If an optional dose is not administered, the unused capsules will be kept in their respective inner envelopes inside of the primary container in the safe for drug accountability.

Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with relevant federal and state regulations.

### **6.5 MDMA Stability**

Complete details on the chemistry, manufacturing, and control of the MDMA to be used are described in Drug Master file (DMF) # 6293. As described in that file, MDMA was prepared for human consumption in 1985 by David Nichols, Ph.D., at the Dept. of Medicinal Chemistry and Pharmacology, Purdue University. The identity and purity of this MDMA was confirmed using High Performance Liquid Chromatography (HPLC) in 1997, as described in DMF # 6293, and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor prior to

starting MAPS' first U.S. pilot study of MDMA-assisted psychotherapy in people with PTSD. The analysis found the MDMA to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart in February 2006, continued to find a high degree of purity. This analysis found the MDMA in question to be 99.9% pure. This MDMA is currently in use in an ongoing investigation of MDMA-assisted psychotherapy in the U.S. It was also used in MP-1, with drug administration ending in 2008, and in a non-sponsor supported study in 2006 [154].

## **7.0 Risks of Participation**

### **7.1 Risks and Discomforts Associated with Non-drug and Experimental Sessions and Assessment of Measures**

In preparation for drug-assisted psychotherapy sessions, blood draws and a full medical examination are required to establish eligibility for the study. Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

During screening, non-drug and drug-assisted psychotherapy sessions and assessment of study measures, subjects will be asked to think about and discuss their thoughts and emotions relating to their illness. They may experience intense emotional responses to recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the process or prospect of illness, death, and dying can produce distress during and immediately after non-drug psychotherapy, experimental, and open-label sessions. Psychotherapy is conducted as part of this study, and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

All psychotherapy sessions will be recorded to audio and video for research and training purposes. Subjects may feel uncomfortable with having their sessions recorded. Subjects may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment and will be used to create a Treatment Manual. Subjects will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by researchers or regulatory agencies.

### **7.2 Risks of Receiving MDMA**

Spontaneously reported reactions and common adverse effects of MDMA are modest and have generally not been associated with serious discomfort by healthy volunteers in previous studies. Common reactions include lack of appetite, insomnia, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry

mouth, ruminations, and thirst. Other slightly less common reactions include restlessness, parasthesias (odd somatic feelings, such as tingling or feeling hot or cold), impaired judgment, perspiration, drowsiness, and nystagmus (eye-wiggling). While anxiety, headache, fatigue, insomnia, and lack of appetite were spontaneously reported by 40% to 80% of subjects in both conditions in MAPS study MP-1 (N=23), tight jaw, nausea, impaired gait/balance, and sensitivity to cold were more often reported by subjects in the MDMA than the placebo condition, and irritability was slightly more likely to be reported in the placebo condition. Additionally, subjects in the MDMA condition were more likely to report muscle tension in various body parts and diarrhea.

These effects are transient and diminish as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, needing more sleep, weakness, heavy legs, dry mouth, low mood, or irritability. Sub-acute effects are reported less often than acute effects. More information on spontaneously reported reactions is described in the IB.

MDMA may produce mild alterations in sensory perception and altered perception of time [36, 92, 155]. Women may be more sensitive to these effects [114]. MDMA acutely affects attention, information processing, and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of complex scene changes [156]. Preclinical data in animals suggests that the profile of neurotransmitter release observed after MDMA administration may increase the risk of mania in some individuals [157], although mania has not yet been a reported side effect of MDMA or ecstasy.

For this reason, subjects will stay at the site overnight and will not be permitted to drive after experimental sessions.

MDMA may produce modest changes in immune functioning, lasting up to 48 hours [158, 159]. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. For this reason, potential subjects with lowered white blood cell counts or other signs of impaired immunity will be excluded from the study.

Further information on the risks associated with MDMA, including information drawn from case reports and studies of ecstasy users, can be found in the IB.

### **7.2.1 Cardiovascular and Sympathomimetic Effects**

The active dose of 125 mg, followed by a supplemental dose of 62.5 mg after one and a half to two and a half hours, is expected to produce significant but transient, self-limited increases in blood pressure and heart rate. These changes should last no more than six hours. In less than 5% of volunteers in Phase 1 studies, peak blood pressure values were higher than 140/90 mmHg. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of subjects and predefined contingency plans will allow

the researchers to rapidly identify and manage any related toxicity. For more information, see the IB.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing hypertension and serious cardiovascular or cerebrovascular illness and monitoring blood pressure and pulse, as described in Section 5.1.2. During experimental sessions, the co-therapists will evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. Subjects reporting chest pain, shortness of breath, neurological symptoms, or other potential indicators of medical complications will have more frequent measurements and assessment by the PI. Any subject who experiences medical complications during an experimental session will not be given another experimental session, unless it is approved by the CI, PI, and the Medical Monitor.

In case of need, subjects will be transferred to the emergency room at the closest hospital, as described in Section 8.4. Reasons for moving a patient to an Emergency Department (ED) would include, but not be limited to, severe headache in the setting of hypertension, angina, or neurological deficits regardless of blood pressure. The CI and PI may, at any time, make a clinical judgment to transfer the patient to the ED for closer monitoring and additional treatment.

The PI will be prepared to respond to rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). The PI will attend to any signs or symptoms of neurological deficit or confusion that is more pronounced than might be expected from MDMA or from psychological distress and will make an on-site evaluation or a decision on whether to initiate transfer to the ED. If any subject has neurological deficits, as assessed by the PI, whether or not they are associated with hypertensive crisis, they will be monitored, as described above. If necessary, the subject will be transported to the emergency department at the closest Hospital for further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be sufficient time to administer recombinant tissue plasminogen within the three-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [160, 161].

The therapists will observe the subject and note any complaints of chest pain. If a subject experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will be transported to the ED or a location in the hospital where appropriate care can be given. The subject will be given 81mg of aspirin to chew if there are no contraindications, and nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the subject has had an AMI, they will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [162].

### 7.2.2 Psychological Distress

Mild anxiety and depressed mood are occasionally reported one to three days after MDMA administration [34, 114, and see the IB]. Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately three to five hours after drug administration) or even later. Anxiety or distress during the session may last for as little as five minutes or for as long as five hours or more. In addition, psychological distress could arise following an MDMA session as a result of subjects having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been self-limiting and have responded well to reassurance from the therapists, with occasional use of benzodiazepines for anxiety. In this study, subjects will have the intention of confronting and working through intense emotions related to their experiences of illness and mortality, or other distressing thoughts and feelings. Accordingly, signs of psychological distress, panic, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

Proper preparation and follow-up support will reduce the difficulties subjects might have with acute or sub-acute reactions. The potential for destabilizing psychological distress will be minimized by:

- Excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders)
- Preparatory non-drug psychotherapy sessions before the experimental session
- Creating an atmosphere of trust during the experimental session
- Close monitoring
- Daily contact with subjects for the period of a week after the experimental session
- Providing non-drug psychotherapy sessions
- Subjects will remain at the study site for the night of each experimental session to further reduce psychological distress. Qualified personnel will be available during the overnight stay to respond to the needs of the subject. Attendants will be instructed to contact the therapists upon request or at the appearance of signs of a potential serious adverse event.

During the preparatory sessions, subjects will be made aware of the fact that difficult emotions, including grief, rage, fear or panic, may arise during experimental sessions. Every effort will be made to help subjects resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the experimental session, including empathic listening on the part of the therapists and performance of diaphragmatic breathing and meditation by subjects.

At the end of the six to eight hour experimental session, if the subject is still severely agitated or experiencing any other severe psychological distress, the following measures will be taken:

- If the subject is anxious, agitated, in danger of any self-harm, or is suicidal at the end of the experimental session, the therapists will remain with the subject for at least two more hours. During this time, the therapists will employ affect management techniques, will talk with the subject to help him or her gain cognitive perspective toward their experiences, and will help the subject implement the self-soothing and stress inoculation techniques presented during the preparatory sessions. If this situation should occur during an integrative session, at least one of the therapists will be available to stay with the subject for at least two additional hours.
- If a subject remains severely anxious, agitated, in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period, the PI will decide between the following options:
  1. A psychiatric nurse, therapeutic assistant, physician, or therapist will stay with the subject until the time of his or her appointment with the therapists the next day. The therapists will then meet with the subject daily until the period of destabilization has passed.
  2. If a subject experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an MDMA session, the therapists may prescribe a “rescue medication” such as a benzodiazepine or zolpidem. If the subject has previously been prescribed opiate medication for pain management, and is experiencing significant pain during this period, the subject will be permitted to administer their medication. This medication will be captured on the concomitant medications CRF page. The physician should not prescribe an SSRI, SNRI, or MAOI in this context, unless it has been determined that the subject will be withdrawn from the study. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the therapists.
  3. Hospitalization for stabilization. If a subject should become psychotic arrangements will be made to stabilize them and transfer them to the ED if necessary.

Subjects hospitalized after a severe panic reaction will be suspended from the protocol until after recovery or stabilization, at which time the CI will carefully evaluate the subject’s emotional status.

For those subjects engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the subject’s outside therapists will be involved in the management of any psychiatric complications. For those subjects engaged in an ongoing psychotherapeutic relationship with the CI, the management of any psychiatric complications will be undertaken by them in their capacity as the subject’s therapist.

### **7.2.3 Body Temperature**

MDMA administered in a controlled setting produces only a slight increase in body temperature [114]. Ambient temperature does not enhance or attenuate this slight elevation in humans.

If temperature rises more than 1° C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature, and, if necessary, directing a fan toward the subject. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, the PI will be consulted for further evaluation and treatment.

#### **7.2.4 Reproductive and Developmental Risks**

Risks posed by MDMA to pregnant women are not known. One of two studies of Ecstasy users suggests that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [163, 164], and a third reported some developmental delays in mothers reporting use of ecstasy and other drugs during pregnancy [165].

Pregnant and lactating women will be excluded from participation in the study. Women who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental session and must agree to use birth control for the treatment portion of the study.

#### **7.2.5 Potential Neurotoxicity Associated with Ecstasy Use**

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [166]. However, they are basing their case on studies that employed inappropriately high doses of MDMA utilized in animal studies and on human studies comparing the effects of repeated use of ecstasy, often along with other drugs. Meanwhile, another recently published meta-analysis has taken careful steps to overcome methodological limitations in previous work and found only modest evidence of neurotoxicity [167]. We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in this study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. More information on the potential neurotoxicity of MDMA can be found in the IB.

#### **7.2.6 Risk Mitigation**

Careful review of medical screening data will be utilized to exclude potential subjects with pre-existing exclusionary medical conditions from the study. Study procedures have been developed to mitigate the risks of receiving MDMA described in detail in the IB. Ambient temperature will be kept at a comfortable level during Experimental sessions. Subjects will not be allowed to drink more than 3L of fluids over the course of the experimental session and fluid intake will be spread out appropriately during the session.

Fluids administered will include electrolytes. If a subject exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an experimental session, they will not be given another experimental session unless it is approved by the CI, PI and the Medical Monitor.

### **7.3 Abuse Liability**

Findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens,” like psilocybin, but lower than that reported for psychostimulants, such as cocaine or methamphetamine. More information on abuse liability is provided in the IB.

To ensure MDMA-assisted psychotherapy does not cause patients to develop symptoms of drug abuse after the treatment period of the study, drug use is monitored during the long-term follow-up. Based on long-term follow-up data from two sponsor-supported studies (N=32), only one subject took Ecstasy after completing the study and failed to reproduce the experience from the study and a number of subjects volunteered that they would never seek out Ecstasy outside a legal, controlled, therapeutic setting. In addition, negative results from MDMA-specific drug testing data obtained from the Swiss study MP-2 (N=12) supports that none of these subjects took Ecstasy outside of the study during the long-term follow-up period.

Diversion is not an issue in this protocol because MDMA will only be administered in a controlled environment under the supervision of the CI and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

## **8.0 Adverse Events**

### **8.1 Adverse Events**

An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a clinical research study subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current IB or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored by the therapists until resolution or, if the AE becomes chronic, a cause can be identified. If an AE is unresolved at the conclusion of the protocol, a clinical assessment will be made by the CI and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the “Adverse Events” CRF will be determined by the PI as:

- Mild: No limitation in normal daily activity
- Moderate: Some limitation in normal daily activity
- Severe: Unable to perform normal daily activity

The relationship of the study treatment to an AE will be determined by the PI based on the following definitions:

1. “Not Related”: The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject’s pre-existing condition.
2. “Possibly Related”: The administration of the investigational product and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational product.
3. “Probably Related”: Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

## **8.2 Spontaneously Reported Reactions**

Commonly expected spontaneously reported reactions are collected on a separate CRF page and will be categorized as mild, moderate, or severe. Common, expected reactions are defined as those most frequently reported in the literature and include: Anxiety, Diarrhea, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Heavy Legs, Impaired Gait/Balance, Impaired Judgment, Increased Irritability, Insomnia, Jaw Clenching or Tight Jaw, Lack of Appetite, Low Mood, Muscle Tension, Nausea, Need More Sleep, Nystagmus, Parasthesias, Perspiration, Restlessness, Rumination (increased private worries), Sensitivity to Cold, Thirst, and Weakness. Spontaneously reported reactions will be collected during the experimental session and the seven days of telephone contact following the integrative session that occurs on the day after each experimental session. Each reported reaction will be actively followed during follow-up phone calls or visits until resolution. Reactions lasting longer than seven days above baseline levels of intensity will be classified as Adverse Events and recorded in the AE log. Any reported event that is not listed on the commonly reported reactions list will be collected as an adverse event following the plan in section 8.6.

## **8.3 Serious Adverse Events**

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e. the subject was, in the opinion of the CI, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e. the event causes substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

AEs which do not fall into these categories are defined as non-serious. It should be noted that a severe adverse event need not be serious in nature and that a SAE need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as a study-related SAE, unless, in the view of the PI, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis, or abortion does not result in an SAE report, unless, in the view of the PI, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

#### **8.4 Medical Emergencies**

Experimental sessions will take place in the PI's home therapy office, located 3.3 miles from Marin General hospital in a residential area. The Study Coordinator will have an office on-site. The treatment room will be comfortably furnished, with an adjacent restroom. An overnight room will also be used following experimental sessions, and there will be space for both the co-therapy team and a night attendant to remain on-site overnight if necessary. The PI will also remain on-site overnight. The study includes access to an emergency medicine specialist if needed. The therapists or PI will be available via mobile phone or pager throughout the study if any problem occurs when a subject is not at the site. Subjects will continue to see their outside therapist throughout the study. For a recently completed Phase 2 trial, the sponsor has established contingency plans for responding to those AEs that appear most likely, based on a comprehensive review of literature described in the current IB. The same contingency plans and equipment will be used in this protocol. The site will provide an Automated External Defibrillator (AED). The therapists will maintain BLS certification.

With these personnel and equipment, the therapists or PI will be able to perform basic cardiac life support if necessary and call Emergency Medical Services (EMS) to transport the subject to the ED at the closest hospital. In the event of a medical emergency or any other medical problem, the PI will be on site during the course of the experimental sessions, or immediately available by phone if the experimental session has concluded, and based on his assessment of the situation, he will make the decision to either evaluate the subject himself at the site, have the therapists call EMS to transport the subject to the ED, or instruct the therapists to take the subject to the ED where he will meet them.

## **8.5 Adverse Event Collection**

The PI will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The therapists will collect AEs during study visits after enrollment.

Adverse events that will be collected for the duration of the protocol are:

- All SAEs will be collected through subject termination.
- All spontaneously reported reactions will be collected on the day of drug administration and for seven days after each experimental session or until they resolve. All reported reactions will be actively followed until they resolve.
- Any reported reactions still above the subject's baseline level of severity after seven days will be classified as Adverse Events and tracked in the AE log.
- All AEs (defined as any adverse event that is not enumerated in the list of commonly reported reactions) will be collected from enrollment through the subject's last one-month follow-up. All adverse events will be actively followed until they resolve.
- Events related to planned treatments or physician visits for baseline conditions collected in the medical history will not be collected, unless there is an exacerbation of the condition, in which case they will be actively followed until resolution.
- Any AE leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study and will be actively followed until resolution.

A Memory Aid Card will be provided to the subject on the last visit prior to the twelve-month follow-up to record information on medications taken to treat SAEs, AEs leading to withdrawal and psychiatric AEs during the follow-up period between the End of Stage 1/Stage 2 and the twelve-month follow-up evaluation. The Memory Aid Card will not be collected, but information from the card will be used to aid the subjects in providing information to the CI. This information may be collected by phone.

All SAEs will be collected for the duration of the protocol. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours of the CI's awareness of their occurrence. All SAE reports should be faxed to the sponsor. A fax number will be provided to the site in

separate site-specific instruction for SAE reporting. In addition to the fax, the PI, CI, or designee should call the CRA during normal working hours and verbally inform the CRA of the SAE. During off business hours or if medical advice is needed immediately, please call the sponsor Medical Monitor. An SAE reporting instruction with all contact numbers will be provided to the site prior to study start.

## **8.6 Medical Monitor**

Michael C Mithoefer  
Email: mmithoefer@mac.com  
Telephone: (843)-849-6899  
Fax: (843)-278-9188

Study Monitor contact information will be provided in a separate contact list.

## **9.0 Concomitant Medications and Tapering Instructions**

The PI will record concomitant medications during screening. If the subject is being treated with psychiatric drugs at the time he or she is recruited into the study, the prospective subject will be encouraged to discuss medication tapering with his or her outside treating physician, if any, and will be required to give the PI permission to do so as well. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA session to avoid the possibility of any drug-drug interaction (the interval will be at least five times the particular drug's half-life, plus one week for stabilization). If applicable, the PI will consult with the prescribing physician concerning drug tapering. If the participant is taking opiates for pain management, then possible reduction in dose prior to experimental sessions will be discussed.

The therapists will request information about any changes in medication just prior to each experimental session. The PI will be responsible for reviewing and confirming all medications collected during the study.

All medications, over the counter (OTC) and prescription, will be collected from screening through seven days after the last MDMA session. From seven days after the last MDMA session through study termination, only prescription or OTC medications taken to treat AEs will be collected. Throughout the protocol all medications used to treat AEs will be collected as specified in Section 8.5 and all changes including discontinuations or additions to psychiatric medications will be collected. Medications will be recorded on the concomitant medications CRF.

Subjects must be willing to refrain from taking any psychiatric medications during Stage 1 and Stage 2, with the exception of gabapentin when prescribed for pain control. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency, as long as they discontinue five half-lives before each experimental session and do not restart for ten days after each experimental session. If the subject is on

opiate medications for pain management, they can continue to use them at the same dose and frequency although they may be asked to decrease the dose or temporarily discontinue use 24 hours before each experimental session if they are able to do so without undue distress. In the event of a pain flare-up during this period, subjects will be permitted to use their prescribed medication as necessary.

**Table 6. Medication Tapering Table**

<b>Generic Name</b>	<b>Brand Name</b>	<b>Half-life (hours) Including Active Metabolites</b>	<b>Days for Washout</b>
alprazolam	Xanax	11	3
aripiprazole	Abilify	75	16
atomoxetine	Strattera	5-24	5
bupropion	Wellbutrin	21	5
citalopram	Celexa	35	8
clonazepam	Klonopin	30-40	8
diazepam	Valium	20-70	15
duloxetine	Cymbalta	12	3
escitalopram	Lexapro	32	7
fluoxetine	Prozac	7-9 (days)	45
imipramine	Tofranil	6-18	4
lamotrigine	Lamictal	25	6
lorazepam	Ativan	12	3
mirtazapine	Remeron	20-40	8
olanzapine	Zyprexa	21-54	11
paroxetine	Paxil	21	5
prazosin	Minipress	2-3	1
quetiapine	Seroquel	6	2
risperidone	Risperdal	3-20	4
sertraline	Zoloft	26	6
temazepam	Restoril	8-12	3
trazodone	Desyrel	9	2
venlafaxine	Effexor	12	3
ziprazidone	Geodon	7	2
zolpidem	Ambien	2.5	<1

The PI may prescribe a designated rescue medication in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management). Rescue medications may include medications such as benzodiazepines or sedative/hypnotics, (eg. lorazepam or zolpidem), or the subject's previously-prescribed opiate medications for pain management. SSRIs, SNRIs, and MAOIs should not be used as rescue medications.

Subjects must agree that, for one week preceding the MDMA session:

- They will refrain from taking any herbal supplement (except with prior approval of the research team).
- They will refrain from taking any prescription or nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs, acetaminophen,

birth control pills, thyroid hormones, or other medications approved by the research team).

Subjects will receive a Memory Aid Card for use between the End of Stage1/Stage 2 visit and the twelve-month follow-up, as described in Section 8.5. Subjects will use this card to record changes in psychiatric medications that they will be asked about at the termination visit. Memory Aids will not be collected. Subjects may return to taking psychiatric medications and discontinue birth control after the final one-month assessment if necessary.

## **10.0 Clinical Laboratory Assessments**

The PI will examine laboratory assessments gathered in screening for assessing subject eligibility. The PI will use a list of normal ranges to conclude whether subjects are eligible for the protocol, and will indicate justification for admitting subjects with abnormal values, after consultation with the Medical Monitor.

The following laboratory assessments will be performed as a part of screening:

**Serum electrolytes and metabolic profile**, which includes:

- ALT/SGPT
- Albumin:globulin (A:G) ratio
- Albumin, serum
- Alkaline phosphatase, serum
- AST/SGOT
- Bilirubin, total
- BUN:creatinine ratio
- Calcium, serum
- Carbon dioxide
- Chloride, serum
- Creatinine, serum
- Globulin, total
- Glucose, serum
- Potassium, serum
- Protein, total, serum
- Sodium, serum

**CBC**, which includes:

- Hematocrit
- Hemoglobin
- MCV
- MCH
- MCHC

- RDW
- Percentage and absolute differential counts
- RBC
- WBC

**Urinalysis**, which includes:

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Occult blood
- Leukocyte esterase
- Nitrite
- Bilirubin
- Urobilinogen

**Thyroid function**, which includes:

- TSH high sensitivity
- Free T4
- Free T3

**HIV serology** will be performed.

A **urine-dip pregnancy test** for females of childbearing potential will be performed. The urinary pregnancy tests and drug tests will be performed at the study site.

The laboratory that will perform assessments, other than the urine drug screen, and pregnancy test is:

LabCorp  
2000 Van Ness Avenue  
San Francisco, CA 94109  
Phone: (415) 409-2563

## **11.0 Study Monitoring, Auditing, and Documentation**

The CI, therapists, and their study staff will be trained prior to the start of the study. The study site will be monitored by site visits and telephone calls to the CI by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment in order to comply with GCP guidelines and to ensure validity of the study data. From the start of the study, videos from selected sessions will be reviewed for development of a

Treatment Manual, therapeutic alliance and inter-rater reliability. Adherence to the protocol will be checked by monitoring and by review of selected video data. During each monitoring visit, source data verification will be performed to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. A CRF collation supplied by the sponsor will be completed for each subject enrolled. Monitoring and auditing procedures will be supplied in a separate document.

During or after the study, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

## **12.0 Data Analysis**

The sponsor will judge the clinical and statistical significance of the study based on a comparison of data collected at Baseline and the Primary Endpoint using the STAI-Trait as the primary outcome measure. Descriptive statistics will be computed overall and within the two conditions for all available data from outcome measures, including minimum, maximum, average, and standard deviation. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, nonparametric statistics will be utilized in the analysis. The sponsor will utilize the results of this pilot study to assess variability of the estimates to determine effect size for the impact of two sessions of MDMA-assisted psychotherapy on standardized clinical outcome measures of anxiety, depression, and quality of life. Effect size of the active treatment will be estimated using Cohen's techniques for all outcome measures for Stage 1, Stage 2, and long-term follow-up.

The sponsor will examine placebo and MDMA groups for homogeneity at baseline through comparing demographic characteristics. There is no expectation that conditions will differ in composition by gender, race or ethnicity, duration of anxiety, or presence versus absence of other permitted psychiatric disorders, such as depression. However, owing to small sample size, such variations may arise by chance.

The sponsor will examine STAI-Trait scores at Baseline and the Primary Endpoint in placebo and MDMA conditions using difference scores, and independent sample t-tests will be used to test for significance between groups, with p value set at 0.05. This is the main analysis for this study.

This study is exploratory. As a result, the sponsor will perform tests on all formal statistical comparisons without correcting for multiple comparisons in order to better detect any indications of change.

Independent T-tests that will compare Baseline to Primary Endpoint difference scores for MDMA and placebo will also be performed on STAI-State scores, MADRS scores, BDI-II scores, FACIT-Sp scores will be tested for significance to detect any changes after two experimental sessions.

Changes in symptoms of anxiety, depression, global function, attitudes toward death, sleep quality, posttraumatic growth, quality of life, self-compassion and mindfulness from the Primary or Secondary Endpoint to one month after the third Stage 1 Experimental Session will be used for an exploratory within-subject analysis with p value set at 0.05 to see whether a third active-dose MDMA session produces further improvements.

Descriptive statistics will be computed for all outcome measures administered during Stage 2. Formal statistical comparisons between Stage 1 and Stage 2 scores may only occur if, at minimum, three subjects complete Stage 2. Data from the open-label third Experimental Session in Stage 1 will be tested for equivalence with Stage 2 data and will be combined with Stage 2 data if found to be equivalent. The sponsor will perform an analysis comparing STAI-Trait and STAI-State scores if STAI-Trait changes significantly, after additional open-label experimental sessions.

The sponsor will examine STAI-Trait scores six and twelve months after the final MDMA-assisted psychotherapy session. If there is enough data available for formal comparisons, the sponsor will examine trends in individual data and will use repeated measures ANOVAs with p value set at 0.05 to compare the one month follow-up STAI-Trait scores, six-month follow-up and 12-month follow-up scores. If there are a greater number of responses from either the six-month or 12-month follow-up, then the follow up with fewer responses may be removed from the repeated-measures analysis for all subjects. Two separate analyses may be performed for each follow up if this occurs. Data from secondary outcome measures will be informally analyzed, comparing results at Baseline, one-month, six-month and 12-month follow-up.

Subjects who discontinue treatment prior to the Primary Endpoint will be asked to complete an outcome assessment prior to continuing to the long-term follow-up. All available data from these subjects will be presented as an exploratory last observation carried forward analysis to examine results without bias towards subjects more likely to complete the study per protocol.

The therapists will record average Baseline and peak and post-drug blood pressure, heart rate, and body temperature for subjects during experimental sessions. The therapists will also record spontaneously reported reactions and AEs, as described in Section 8.5. Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The sponsor will compare peak blood pressure, heart rate, and body temperature for subjects after sessions with placebo or active dose MDMA whenever possible. Descriptive statistics will be computed for CSSRS scores prior experimental sessions and participant mean and maximum CSSRS ideation and behavioral scores. If applicable, the sponsor may examine vital signs in relation to medical diagnoses to further determine the safety of MDMA within this population. Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs.

Responses to the SOCQ and PPQ will be collected. The sponsor will compute descriptive statistics for SOCQ and PPQ scores after each MDMA-assisted psychotherapy session, and average scores for each measure for blinded experimental sessions will be compared between conditions. The data will be explored for effects of condition on domain scores in the SOCQ. If MDMA significantly reduces trait anxiety when compared with placebo, the sponsor will correlate STAI-Trait with scores on the PPQ and SOCQ to determine whether experiencing a non-ordinary state of consciousness or any facet of this state is associated with a change in anxiety symptoms.

An interim analysis may be completed when all subjects have completed Stage 1 and Stage 2, but not all subjects have completed the twelve-month follow-up evaluation. Additionally, an interim analysis may be performed after all subjects have completed Stage 1, but not necessarily before all eligible subjects complete Stage 2. This analysis will address safety, efficacy, and process measures. Results of the interim analysis will have no effect on study conduct.

The sponsor will collect Observer Form and PTGI-Caregiver measures completed by the participant's selected support partner(s) at baseline, primary endpoint and each subsequent endpoint up through 12 month follow up. If more than one support partner completes community ratings, the scores will be averaged for a given time point. The sponsor will compute descriptive statistics for the PTGI-Caregiver and any quantitative responses on the Observer Form. Participant and support partner responses at the same administration time will be compared with a correlational analysis or, if applicable, a non-parametric analysis of equivalence, such as the chi square. The sponsor will compare PTGI-Caregiver and quantitative Observer Form scores from the placebo and active dose MDMA conditions following the same procedures used for participant PTGI responses. If the main analysis of anxiety symptoms detects a significant between-group difference in reduction in anxiety symptoms and if participant and caregiver PTGI responses, then the sponsor will correlate PTGI-Caregiver scores with STAI-Trait and STAI-State to see if significant other observations are also related to changes in anxiety symptoms.

The sponsor will compute descriptive statistics concerning participant and investigator beliefs concerning condition assignment to determine strength of the study blind.

## **12.1 Statistical Power**

The sponsor will utilize the results of this pilot study to collect estimates of effect size for the impact of two sessions of MDMA-assisted psychotherapy on standardized clinical outcome measures of anxiety, depression, and quality of life. The study is likely to be underpowered for detection of differences of a small or moderate effect size and it may detect differences if the effect size is large. When completed, it will be the first study to investigate the effects of MDMA-assisted psychotherapy in people with anxiety arising from confronting a life-threatening illness. There are no previous studies on which to estimate effect size for these findings.

Analyses of MAPS' completed U.S. study of MDMA-assisted psychotherapy in twenty people with PTSD found an effect size of 1.24 for treatment efficacy, as represented by changes in CAPS score [168]. The degree to which symptoms of anxiety and depression will respond in a similar fashion is currently not known. Narrative reports suggest symptomatic reduction and improvement in quality of life but do not provide information for computing effect size.

### **13.0 Ethics**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21) and with the ethical principles laid down in the Declaration of Helsinki.

The protocol and the ICF must be reviewed and approved by a properly constituted IRB and FDA before study start. Signed and dated documentation of IRB and FDA approvals must be provided to the sponsor. Prior to study start, the PI is required to sign a protocol signature page confirming her/his agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor.

### **14.0 Informed Consent**

The main licensed therapists are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. Information about the study must be given orally and in an understandable form. Written information about the trial will also be provided. The informed consent document will be provided to the subject in advance of the informed consent discussion, with enough time provided for the subject to review the document in an environment of their own choosing. The informed consent discussion must be conducted by a person who is qualified according to FDA regulations. The subject should have the opportunity to inquire about details of the MDMA session and to consider participation. A witness must be present for the informed consent process, and must sign the informed consent document as well. Individuals who are being treated in the CI's private therapy practice may participate in the study. In these cases, another physician will conduct an independent review of these participants' eligibility and administer informed consent procedures.

In addition to the explanation of study visits, the information should include that access to original medical records and processing of coded personal information must be authorized. Written consent to take part in the study includes giving the CIs permission to view the subject's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

Eligible subjects may only be included in the study after signing the IRB approved ICF. Informed consent must be obtained before conducting any study-specific procedures (i.e.

all of the procedures described in the protocol, including screening activities). The process of obtaining informed consent should be documented in the subject Source Records. The therapists will provide a copy of the signed ICF to the subject and will maintain the original in the ISF. Support partners and individuals close to the subject who will be completing measures will also be required to sign a brief Informed Consent document.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised ICF and written information should receive approval from an IRB before use. The subject should be informed in a timely manner if new information becomes available that may affect the decision to take part in the MDMA-assisted session. The communication of this information should be documented. Subjects can withdraw consent at any time without prejudice. If a subject withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, the CIs will have full access to the subject's medical records, including termination visit information. If a subject revokes only the HIPAA authorization, the CIs will have full access to all of the subject's medical records prior to the date and time of revocation.

## **15.0 Confidentiality**

Every effort will be made to strictly safeguard the confidentiality of subjects in their role as research subjects. Removing identifying information from data and restricting access to researchers directly involved in assessing the subjects should prevent the dissemination of confidential data, with or without identifying information. Except for the screening log, the informed consent and a subject contact information sheet that will be stored separately from other documents, all data will be identified only by the subject's initials on the source document and five-digit subject number. If past medical records are needed, subjects will sign forms for the release of information upon consent to permit screening for protocol enrollment. Copies of audio and video recordings intended for sharing with subjects will only be marked with the subject's subject number. Any materials mailed to subjects will be sent along with stamped return envelopes using the office address of the PI both as main and return address. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the CIs who are directly involved in the protocol, with access to data will not be provided with any information that would identify subjects by name or by other means, such as social security number.

All psychotherapy sessions will be recorded to video and audio. These recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted psychotherapy. They are intended to record the events occurring during therapy, and will not serve as outcome measures. Full names and addresses will not appear in these recordings. They will be maintained on a secure, HIPAA-compliant server.

## **16.0 Costs to Subjects**

There will be no costs to the study subjects. The sponsor will cover all costs of study participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation. Charges for treatment of the subject's condition that are unrelated to the research study or any of its procedures will continue to be billed to the health insurance provider of the subject or to the subject him or herself. It is anticipated that there will not be any charges for treatment that is unrelated to the study except in the case of subjects who previously received therapy from the CIs and who will continue to receive ongoing treatment that is not related to participating in the study.

## **17.0 Treatment and Compensation for Study Related Injury**

Treatment of a study-related emergency would first be billed to a subject's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a subject's health insurance. Some study-related emergencies can be treated by the PI, as described under Section 8.4. If the PI cannot treat a study-related emergency, then there are contingency plans for the transport of subjects to the nearest hospital.

## **18.0 Record Retention**

The PI must retain all study records required by the sponsor and applicable ICH-GCP and FDA regulations in a secure and safe facility. The PI must consult a representative of the sponsor before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to ICH-GCP regulations in the ISF. It is the responsibility of the sponsor to inform the PI or institution as to when these documents no longer need to be retained.

## **19.0 Publication Policy**

The sponsor recognizes the importance of communicating medical study data and therefore encourages publications in reputable scientific journals and presentations at seminars or conferences. It is understood by the CIs that the information generated in this study will be used by the sponsor in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the CI is obliged to provide the sponsor with complete test results, all study data, and access to all study records.

Any results of medical investigations with the sponsor products and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the PI and the sponsor clinical research representative(s) prior to submission for publication or presentation. Due regard shall be given to the sponsor's legitimate interests, e.g. manuscript authorship, obtaining optimal patient protection, coordinating and

maintaining submissions to health authorities, and coordinating with other ongoing studies in the same field.

The full details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Study Agreement.

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